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Medication induced diabetes

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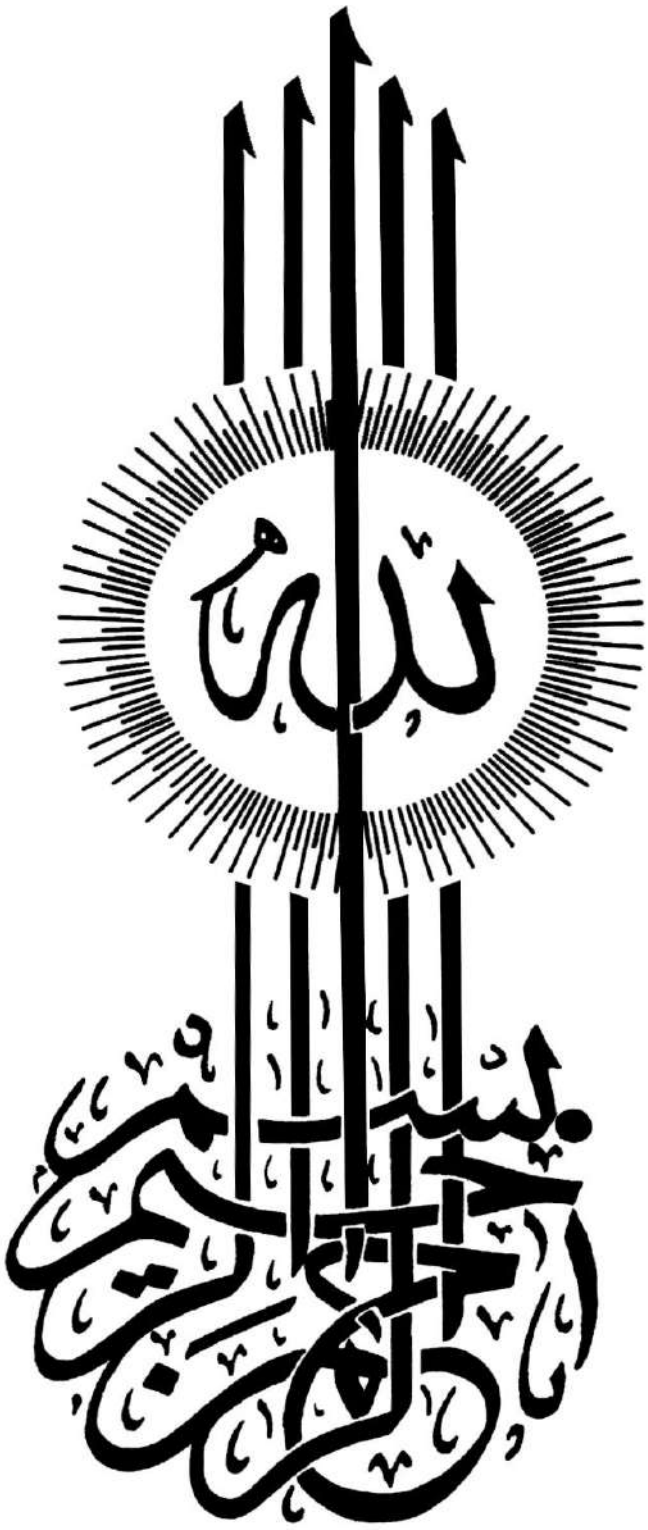

راقب أفكارك ، لإنها ستصبح كلماتك

راقب كلماتك لانها ستصبح افعالك

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راقب عاداتك ، لانها ستصبح شخصيتك

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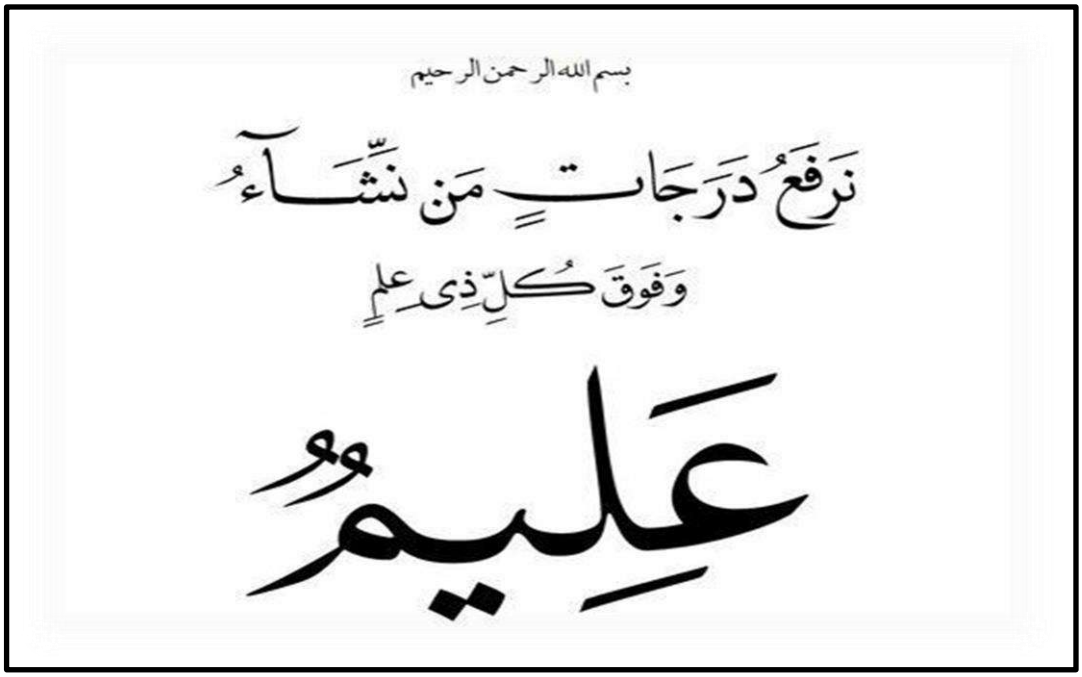

بسم الله الرحمن الرحيم
نَرفَعُ دَرَجَاتٍ مَن نَّشَآءُ
وَفَوقَ كُلِّ ذِى عِلمٍ
عَلِيمٌ

((لايمكن للمرء أن يحصل على المعرفة ألا بعد أن يتعلم كيف يفكر))

كونفوشيوس

الإهداء

الحمد والشكر لله سبحانه وتعالى، والصلاة والسلام على من بلغ الرسالة وأدى الأمانة ونصح الأمة إلى نبي الرحمة سيد الخلق أجمعين نبينا محمد صلى الله عليه وعلى آلة الطيبين الطاهرين . إذا كان الإهداء يعبر ولو يجزء من الوفاء، فالإهداء ....

إلى من أُفضِّلها على نفسي، ولِمَ لا فلقد ضحَّت من أجلي

ولم تدَّخر جُهدًا في سبيل إسعادي على الدَّوام

(أُمِّي الحبيبة).

نسير في دروب الحياة، ويبقى من يُسيطر على أذهاننا في كل مسلك نسلكه

صاحب الوجه الطيب، والأفعال الحسنة.

فلم يبخل عليَّ طيلة حياته

(والدي العزيز).

إلى أصدقائي، وجميع من وقفوا بجواري وساعدوني بكل ما يملكون، وفي أصعدة كثيرة

أُقدِّم لكم هذا البحث، وأتمنَّى أن يحوز على رضاكم

الشكر والتقدير

شكر وامتنان

نحمد الله العلي القدير حمداً يستحقه جلاله وجهه الكريم ونشكره سبحانه على فضله ونعمائه والصلاة والسلام على خير رسله وأنبيائه محمد صلى الله عليه وآله وسلم وعلى من سار على خطاه واتبع سبيل رشده... وبعد

نسأل الله العلي القدير ونرجوه مخلصين إن يتحقق في هذا الجهد المتواضع الفائدة للمهتمين والدارسين وهذا العمل ما كان ليخرج إلى النور لولا توفيق الله سبحانه وتعالى أولا ثم رعاية ودعم ابائنا والوقوف معنا دائما ومساندتنا في توفير كل متطلباتنا واحتياجاتنا منذ نعومة أظافرنا وحتى يومنا هذا وايضا بفضل توجيه ومساعدة المشرفه على البحث استاذتنا الفاضلة الدكتورة (ناديه حسن كاظم) على مساندتنا وإرشادنا بالنصح والتصحيح وعلى اختيار العنوان والموضوع، وتوجيهاتها السديدة التي أغنت البحث وأظهرته بالشكل الذي هو عليه وان ما فيه من جوانب ايجابية فتحسب لها وما فيه من جوانب ضعف فتحسب على الباحثين.
كما نتقدم بالشكر الجزيل إلى لكل من نصحنا أو أرشدنا أو وجهنا أو ساهم معنا في إعداد هذا البحث بإيصالنا للمراجع والمصادر المطلوبة في أي مرحلة من مراحله كما أن شكرنا موجه الى ادارة كلية الصيدلة جامعة بابل للمجهودات المبذولة من قبل أساتذتنا الكرام في الجامعة وأخيرا نسأل الله الهداية والتوفيق للجميع وأن يكون في هذا الجهد علم ينتفع به والله ولي التوفيق..

والحمد لله رب العالمين.

ABSTRACT

Several Epidemiological studies have suggested that rate of development of diabetes mellitus consequent to taking diverse types of medication is increasing now a days. Several medications have been found to be associated with causation of diabetes. Various pharmacological medications which are commonly used in clinical practice are found to affect glucose homeostasis and interfere with the balance between various hormones like insulin, glucagon, catecholamines, growth hormone, and cortisol. Mechanism for the diabetes caused due to medications is associated with a reduction in insulin production, some with reduction in insulin sensitivity, and some appear to be associated with reduction in insulin production along with the insulin sensitivity. It is very difficult to establish a precise cause and effect relationship between a medication and development of diabetes. Various clinical studies of medications typically concentrate on evaluation of effectiveness and are not powered to evaluate side effects. Several covariant such as the weight gain associated with medication such as steroids or antipsychotics also make it difficult to find that whether the development of diabetes was a primary or secondary effect of the medication. Mechanisms for the causations of diabetes have been linked with range from decreased insulin secretion to decreased insulin action to direct neural effects. Stopping or switching medication is considered as the first step in treating the drug induced diabetes. While the information to support many of the consensus recommendations for treatment drug-induced diabetes is lacking. To establish the optimal therapy for Drug induced diabetes, it is quite essential to understand the potential mechanism which interrupts the metabolism of carbohydrates

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic

hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases. Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors, meglitinide analogues, and thiazolidenediones. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological). The main side effects are weight gain and hypoglycaemia with sulfonylureas, gastrointestinal (GI) disturbances with metformin, weight gain, GI disturbances and liver injury with thiazolidinediones, GI disturbances, weight gain and hypersensitivity reactions with meglitinides and .flatulence, diarrhoea and abdominal bloating with alpha-glucosidase inhibitors

In clinical practice, commonly used drugs may interfere with glucose homeostasis and provoke impaired glucose tolerance, hyperglycaemia or new-onset diabetes mellitus, or may worsen glycaemic control in individuals with

diabetes . These adverse events occur especially in individuals with a predis- position due to their genetic background and/or unfavourable environment upon which the deleterious effects of the medications are superimposed. Pharmacogenomics can regulate the expression of genes involved in signalling pathways related to the pharmacokinetics or pharmacodynamics of drugs or the pathogenesis of diabetes, thus contributing to potential interindividual differences in drug-induced glucose impairment . Drug-induced diabetes is now .recognised as a component of secondary diabetes

Numerous pharmacological compounds can alter glucose homeostasis by different mechanisms: reduced tissue insulin sensitivity via intrinsic direct mechanisms; promotion of weight gain; and/or functionally impaired insulin secretion. Some also increase hepatic glucose production, induce acute pancreatitis or even exert direct cytotoxic effects on pancreatic beta cells . The present concise narrative review will focus on four important pharmacological classes:(glucocorticoids (GCs); antipsychotics; betablocker ,thiazide diuretic ,statin) .These drug classes were selected because of their increasing use in clinical practice and their potential risk for severe hyperglycaemia/diabetes. Other medications, such as statins, merit attention because they are widely used in individuals with or at risk of diabetes. A meta-analysis of 14 trials. suggested a 9-33% higher risk of new-onset diabetes with statin use. However, any deterioration of glucose control is generally mild, including that occurring in individuals with diabetes. The underlying diabetogenic action of statins likely results from a complex interplay between pancreatic and extrapancreatic effects. Nevertheless, cardiovascular protec- tion by statin treatment outweighs the risks associated with development of new-onset diabetes or modest . deterioration of glucose control in individuals with diabetes

Of note, transient reversible (sometimes severe) hyperglycaemia should be distinguished from true diabetes with sustained (but less severe) hyperglycaemia. High doses of GCs given for a short period may result in severe acute but reversible hyperglycaemia; low doses of GCs, antipsychotics and antiretrovirals given as long-term treatments may result in diabetes-related long-term complications. Drug-induced diabetes may be reversible if the medication is discontinued; however, it may be permanent, depending on the characteris- tics of the drug therapy (medication, dose, duration) or the patient's

background profile (age, body weight, family history). Proposals for the medical surveillance and management of drug-induced diabetes are very similar to recommendations

1-Clinicians should be aware of the risk of new- onset diabetes or worsening of diabetes when prescribing some drugs, especially in individuals already at risk

2-Focus should be on glucocorticoids, statin therapy, new-generation antipsychotics and betablocker and thiazide diuretic

3-Because of different underlying mechanisms, both prevention and treatment may differ be- tween the five studied pharmacological groups

4- Drug-induced weight gain (abdominal adiposity and 'adiposopathy') contributes to disturbances in glucose homeostasis

5- Lifestyle (diet and exercise) recommendations should be reinforced in individuals who receive drugs that could lead to weight gain and diabetes

6- Pharmacotherapy of drug-induced diabetes is similar to that of other forms of diabetes, with a stepwise approach from metformin to insulin if required

for other types of diabetes (especially type 2 diabetes), focus- ing on lifestyle (diet and exercise) and, if necessary, stepwise glucose-lowering treatment, usually starting with metformin. Only specific aspects relating to each drug class that differ from the classical management of individuals with diabetes will be

discussed

Table 1

Medications Associated With Hyperglycemia or Diabetes Mellitus

Drug Class	Agents	Mechanism	Incidence of Drug-Induced Diabetes or Hyperglycemia	Short-Term Reversibility
Steroids	Prednisone Prednisolone Methylprednisolone Dexamethasone	Insulin resistance, increased hepatic glucose production, increased PPAR-gamma activation	40%-65%	Yes
Antipsychotics	First generation: Chlorpromazine, perphenazine, phenothiazines Second generation: Clozapine, olanzapine, Paliperidone, risperidone, quetiapine	Insulin resistance, reduced insulin secretion, beta-cell damage	10%-30%	Yes
Antiretrovirals	Protease inhibitors: Atazanavir Darunavir Indinavir Lopinavir Nucleoside reverse transcriptase inhibitors: Zidovudine Stavudine	Decreased insulin sensitivity, insulin resistance, lipodystrophy, metabolic syndrome	3%-17%	No
Chemotherapy	Alpelisib PD-1/PDL1 checkpoint inhibitors: • Pembrolizumab • Nivolumab • Dostarlimab • Atezolizumab • Avelumab	Alpelisib: decreased insulin resistance PD-1/PD-L1 checkpoint inhibitors: autoimmune destruction of pancreatic beta cells	Alpelisib: 63% PD-1/PD-L1 checkpoint inhibitors: 0.8%-1.9%	Alpelisib: yes PD-1/PD-L1 checkpoint inhibitors: no
Transplant immuno-suppressants	Tacrolimus Cyclosporine Basiliximab Sirolimus Everolimus	Decreased insulin secretion, glucose intolerance	15%-30%	Yes
Thiazide diuretics	Chlorthalidone Hydrochlorothiazide Indapamide Chlorothiazide	Reduced potassium leading to decreased insulin secretion, increased insulin resistance	10%	Yes
Lipid-lowering agents	Niacin Statins: • Atorvastatin • Rosuvastatin • Pravastatin • Lovastatin • Simvastatin • Pitavastatin • Fluvastatin	Niacin: altered hepatic glucose metabolism Statins: decreased insulin secretion, decreased glucose uptake in skeletal muscles, insulin resistance	Niacin: 6.8%-19.8% Statins: 7%-48%	Niacin: yes Statins: unknown

Continued

Table 1

Medications Associated With Hyperglycemia or Diabetes Mellitus (continued)

Drug Class	Agents	Mechanism	Incidence of Drug-Induced Diabetes or Hyperglycemia	Short-Term Reversibility
Beta-blockers	Atenolol Metoprolol Propranolol	Decreased insulin sensitivity, decreased insulin secretion, increased glucose production	22%	Yes

PD-1: programmed cell death-1; PD-L1: programmed cell death ligand; PPAR-gamma: peroxisome proliferator-activated receptor gamma. Source: References 3-7.

Mechanisms of hyperglycemia

Mechanisms involved in medication-induced hyperglycemia include ß cell destruction,decreased insulin secretion and/or sensitivity, and excessive glucose influx .The majority of drugs associated with hyperglycemia affect insulin production, secretion, or action, leading to an imbalance in insulin and glucose homeostasis

1 -β cell destruction

β cells can be destroyed by multiple mechanisms. including direct cytotoxicity on pancreatic β cells, inflammation, and islet autoimmunity. Evidence on increased islet cell autoimmunity with certain medications has been emerging. Many pharmacotherapies,particularly newer anticancer medications, modulate immune checkpoint proteins, modify T cell regulatory function, and increase the risk of immune-mediated endocrinopathies including diabetes mellitus.

2- Decreased insulin secretion

Hyperglycemia induces a series of intracellular signals that result in the release of insulin secretory granules that were previously synthesized, processed and stored. Medications that affect the body's ability to adequately synthesize and .secrete insulin result in hyperglycemia

3- Decreased peripheral insulin sensitivity

When insulin reaches target tissues, it binds to a cell membrane receptor that induces a conformational change and activation of intracellular signals. This

results in inhibition of glycogenolysis and gluconeogenesis, increased glucose transport to fat and muscle tissue, and stimulation of glycogen synthesis. Drugs that reduce the receptor number or affinity, interfere with insulin action, or inhibit postreceptor events can cause hyperglycemia by decreasing insulin sensitivity. In addition, some drugs decrease insulin sensitivity in target tissues through indirect mechanisms such as weight gain, leading to obesityinduced .insulin resistance

4-Excessive glucose influx

There are several physiologic processes that release glucose into the circulation ,(eg, hepatic glycogenolysis hepatic gluconeogenesis) while others (eg

glycogen synthesis) remove glucose. Medications that enhance glycogenolysis or gluconeogenesis may resultin hyperglycemia. In addition, excessive glucose intake, particularly through a parenteral route, may overwhelm the pancreatic capacity of insulin production and cause hyperglycemia

Multihit hypothesis

Hyperglycemia does not occur in all individuals exposed to diabetogenic drugs but it is more common when several factors are involved, including;

1- Host-specific factors such as obesity, insulin resistance or β cell autoimmunity

2- High doses of diabetogenic medications or multiple medications that affect glucose metabolism(additive effect)

3- Environmental influences (eg, diet , stress, illness, lack of physical activity)

♫ For some medications, efforts directed at identifying individuals at risk of developing drug-induced hyperglycemia are hindered by its sporadic occurrence. Conversely, risk factors have been better described in patient populations and for medications associated with a

higher incidence of hyperglycemia. For example, among children with acute lymphoblastic leukemia (ALL), those with older age, obesity, and family history

of diabetes have higher probability of developing hyperglycemia.clinical ,condition evolves, often, different compounds

routes of administration, schedules, and doses are used. In addition, other medications, stress, inflammation, and underlying β cell dysfunction may have additive effects. Finally, with a few exceptions, hyperglycemia is poorly

documented as priority is given to the condition that required the use of steroids

The effect of Hyperglycaemia on the immune system

Hyperglycaemia impairs phagocyte function and granulocyte germicidal activity by inhibiting such functions as cell migration to the site of infection, cell adhesion, oxidative burst, and the killing of absorbed bacterial particles. Hyperglycaemia also causes the inhibition of interleukin 2 production, which stimulates T cells and NK cells. High serum glucose level also causes excessive lymphocyte apoptosis and inhibits T-cell proliferation due to decreased .expression of adenosine kinase

Mechanisms that impair the immune response due to hyperglycaemia include the acceleration of non-enzymatic glycosylation of human body proteins. One of the proteins subjecting to non-enzymatic protein glycosylation is immunoglobulin G. Glycosylation impairs the functions of immunoglobulins, which are involved in the immune response to encapsulated bacterial infection. Immunoglobulins stimulate phagocytosis by coating the bacteria and presenting the Fc region to phagocytes. Subsequent proteins that undergo non-enzymatic glycosylation due to hyperglycaemia are components of the comple-ment. This process also impairs their function thereby inhibiting the immune .system

Patients undergoing steroid therapy are immunocompromised patients due to the mechanism of corticosteroid activity and also due to underlying diseases such as acute lymphoblastic leukaemia, severe aplastic anaemia, or lymphoma. Immunosuppression in combination with steroid-induced hyper- glycaemia .may lead to an increased risk of severe bacterial and fungal infections

1-Corticosteroids

Since their discovery, corticosteroids have been used in almost all areas of medicine and by nearly every route. Corticosteroids are synthetic analogs of the natural steroid hormones produced by the adrenal cortex and include glucocorticoids and mineralocorticoids. The synthetic hormones have varying degrees of glucocorticoid and mineralocorticoid properties. Glucocorticoids are predominantly involved in metabolism and have immunosuppressive, anti-inflammatory, and vasoconstrictive effects. While mineralocorticoids regulate electrolytes and water balance by affecting ion transport in the epithelial cells ..of the renal tubules

They have both endocrine and nonendocrine indications. Their endocrine role is often in the diagnosis of Cushing syndrome or the management of adrenal insufficiency and congenital adrenal hyperplasia. Their nonendocrine role regularly takes advantage of their potent anti-inflammatory and immunosuppressive effects to treat patients with a wide range of immunologic and inflammatory disorders. Corticosteroids are used at physiologic doses as replacement therapy in cases of adrenal insufficiency and supraphysiologic .doses in treatments for anti-inflammatory and immunosuppressive effects

The term corticosteroids in practice, however, is generally used to refer to the glucocorticoid effect. Glucocorticoids are primary stress hormones that regulate a variety of physiologic processes and are essential for life. Corticosteroids are among the most widely prescribed drug classes worldwide .

♦ Common indications for corticosteroids, by field, include

1- Allergy and Pulmonology: asthma exacerbation, COPD exacerbation, anaphylaxis, urticaria and angioedema, rhinitis, pneumonitis, sarcoidosis, .interstitial lung disease

2- Dermatology: contact dermatitis, pemphigus vulgaris

3- Endocrinology: adrenal insufficiency, congenital adrenal hyperplasia

4- Gastroenterology: inflammatory bowel disease, autoimmune hepatitis

5- Hematology: hemolytic anemia, leukemia, lymphoma, idiopathic thrombocytopenic purpura

6- Rheumatology: rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, polymyalgia rheumatica

7- Ophthalmology: uveitis, keratoconjunctivitis

8 - Other: organ transplantation, antenatal lung maturation, nephrotic syndrome, cerebral edema, multiple sclerosis

Clinical Metabolic Consequences of GC Overexposure

GCs induce hyperglycemia and glucose intolerance and are responsible for 2% of diabetes, called steroid-induced diabetes. Long-term GC-induced metabolic adverse effects include weight gain; deleterious fat redistribution, and increased free fatty acid circulation; reduction of muscle mass and massive release of amino acids; enhanced gluconeogenesis and endogenous glucose production; bone mass loss and higher fracture risk; most of these features are caused directly by the negative impact of GCs on pancreatic endocrine functions and peripherical insulin sensitivity.

GC molecule	Equivalent dose (mg)[a]	Anti-inflammatory activity (relative to hydrocortisone)	Biological $t_{½}$ (h)
Hydrocortisone	20[b]	1	8–12
Prednisone	5	4	12–36
Prednisolone	5	4	12–36
Deflazacort	5	4	<12
Triamcinolone	4	5	12–36
Methylprednisolone	4	5	12–36
Dexamethasone	0.75	30	36–72
Betamethasone	0.6	25	36–72

Anti-inflammatory activity is expressed relative to that of hydrocortisone, which has been arbitrarily set to 1

[a] For a so-called equivalent dose, the hyperglycaemic effect appears almost comparable between the different GCs, yet few direct comparative studies are available [10]

[b] Twenty milligrams of hydrocortisone correspond to the endogenous daily production of cortisol

The pathophysiology of glucocorticoid-induced hyperglycemia involves multiple mechanisms:

1- increased insulin resistance

2- increased gluconeogenesis

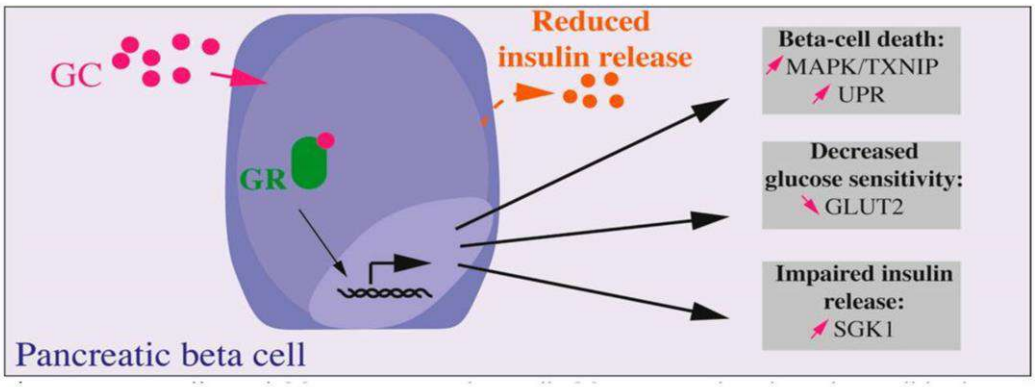
3-.decreased insulin production

4-Glucocorticoids inhibit appetite suppression leading to increased weight gain and insulin resistance.

Pathophysiology/mechanisms

The pathophysiology of glucocorticoid-induced hyperglycaemia and insulin resistance involves multi-organ crosstalk. Glucocorticoids increase appetite and promote the intake of high-calorie (high-fat and/or high-sugar) 'comfort food', which indirectly promotes obesity and diabetes mellitus. Glucocorticoids upregulate the transcriptional and functional activity of neuropeptide Y (NPY)-agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus and promote leptin resist- ance. Skeletal muscle atrophy results from glucocorticoid-mediated protein degradation and decreased protein synthesis in myocytes, and glucocorticoids also decrease glucose uptake into these cells. In the liver, glucocorticoids act directly to upregulate enzymes involved in gluconeogenesis and promote hepatic insulin resistance, which together accelerate the development of hyperglycaemia. Furthermore, glucocorticoids synergize with insulin to stimulate non-esterified fatty acid (NEFA) uptake by hepatocytes and tri- glyceride synthesis in the liver, which causes hepatic steatosis. In adipose tissue, glucocorticoids increase adipogenesis, de novo lipogenesis and triglyceride synthesis as well as lipid uptake and storage. Concurrently, glucocorticoids facilitate lipolysis, which pro-motes the futile cycling of lipids. Glucocorticoids also decrease glucose uptake into adi- pocytes. Acute exposure of pancreatic B-cells to glucocorticoids can stimulate insulin secretion and B-cell hyperplasia to counterbalance glucocorticoid-induced insulin resistance and to maintain plasma levels of glucose within the physiological range. However, long-term exposure to glucocorticoids can interfere with insulin biosynthesis and secretion and induce B-cell apoptosis. Osteocalcin is secreted by osteoblasts and circulating osteocalcin from bone promotes insulin secretion by B-cells. Glucocorticoids suppress the expression of osteocalcin, thereby indirectly inhibiting insulin

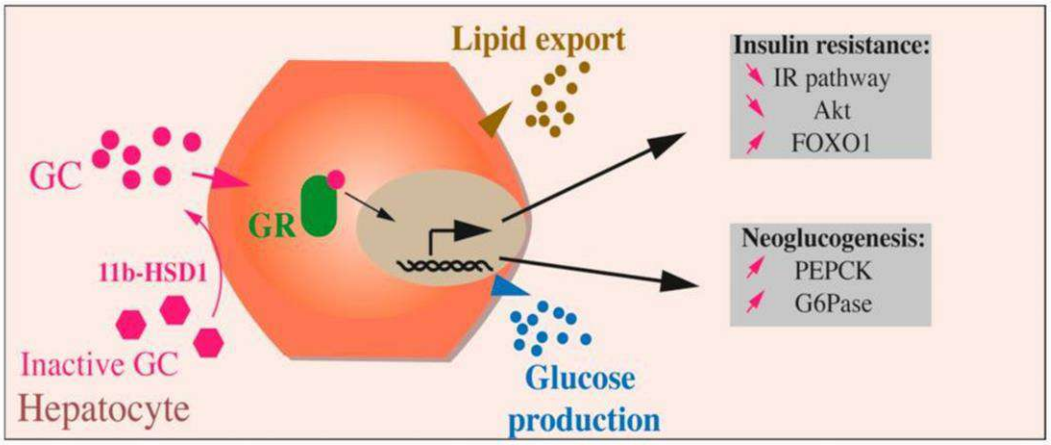
secretion. The increase in circulating levels of amino acids from muscle breakdown and NEFAs and glycerol from adipose tissue lipolysis provide substrates to the liver for gluconeogenesis. High plasma levels of NEFAS also accumulate ectopically in skeletal muscle, liver and B-cells, which further exacerbates insulin resistance. Thick solid arrows indicate effects; thin solid arrows indicate a transition in time; dashed arrows indicate secreted factors



. Direct effects of GC on pancreatic beta cell. GC exposure directly on beta cell leads to altered beta cell function, decreased glucose sensitivity, and insulin secretion and, *in fine*, to beta cell death. Most of the presented results were obtained in vitro, on isolated islets, primary beta cells, or beta cell lines.

GC Effects on Liver Function

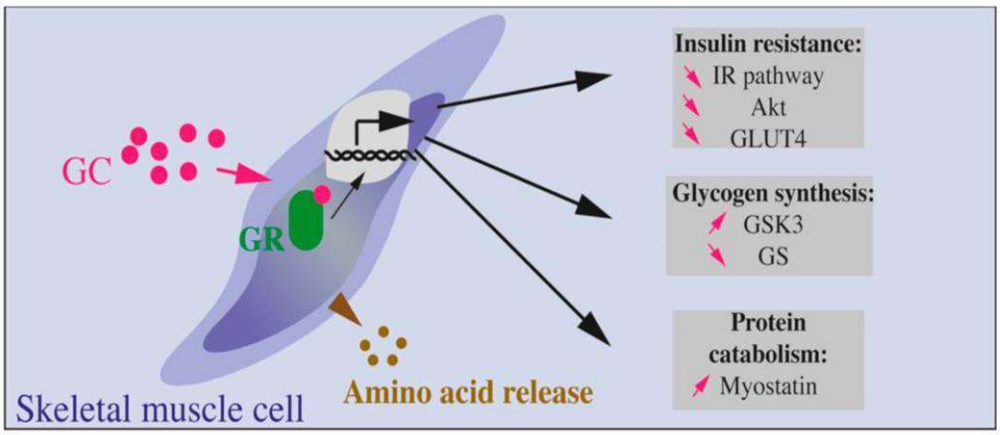
The physiological neoglucogenic role of GC is essential for the transition from an anabolic to a catabolic state, during fasting, but when their production is deregulated, or when the GR pathway is over-activated, the physiological actions are disrupted, leading to liver insulin resistance with glucose overproduction and increased blood glucose levels with an associated lipogenesis, causing hepatosteatosis. In the liver, the activation of the GC-GR signaling pathway inhibits the IR pathway and Akt activity and induces FOXO1, which in turn stimulates PEPCK and G6Pase expression and, ultimately, glucose production



. Effects of GCs on hepatocytes. Inactive GCs are activated through the action of 11b-HSD1. GCs binding to their receptor (GC receptor, or GR) leads in hepatocytes to glucose production through upregulation of neoglucogenesis (augmented PEPK and G6Pase), to lipids export and insulin resistance through reduced IR pathway, Akt activation, and increased FOXO1.

GC Effects on Skeletal Muscles

In muscles, GCs decrease insulin action through many molecular targets such as IRS-1, PI3kinase, AKT, GSK3. Altogether, these proteins are modified by GC exposure ultimately leading to decreased GLUT4 translocation to the plasma membrane, decreased glucose transport, and protein catabolism (Figure 4)

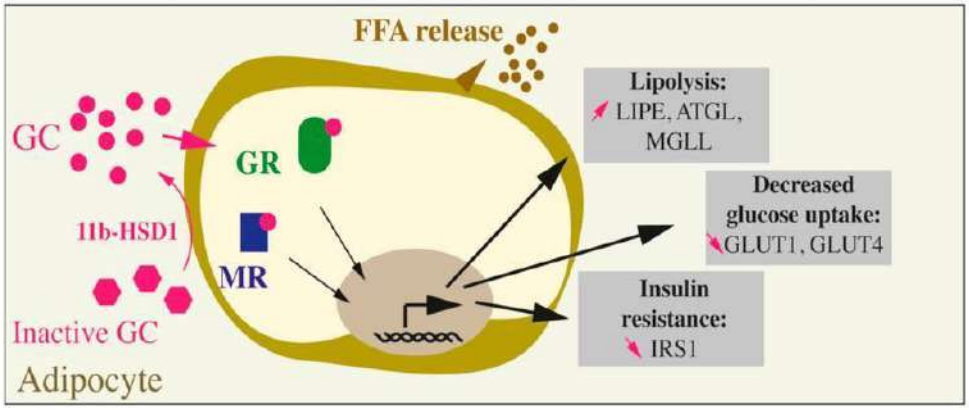


. Effects of GCs on skeletal muscle cells. GCs bind to their receptor (GC receptor, or GR) and lead to protein catabolism (involving increased myostatin production) and amino acids release. Glycogen synthesis is reduced through increased GSK3 and reduced GC. Finally, insulin resistance is also induced by GCs through reduced Akt, GLUT4, and IR pathway.

Impact of GCs on Adipose Tissue

In humans and rodents, chronic GC exposure leads to adipose tissue insulin resistance, macrophage recruitment in the adipose tissues, an increase in the

VAT, a reduction in the SCAT and an increase in lipolysis, characterized by FFA release in the circulation and ectopic storage of fat depots in liver, skeletal muscles and pancreas. The detrimental effects of GCs are mediated by both the GR and the MR as demonstrated by the use of pharmacological antagonists or adipocyte-specific GR- and MR-KO in vivo and in vitro. At the cellular level, GCs increase adipocyte lipolysis via an increase in the expression of lipases (LIPE, ATGL, MGLL), a decrease in the glucose uptake via the down- regulation of the GLUT1 and GLUT4 transporters, and induce insulin resistance via a decrease in IRS1 expression and activity. On the contrary, in preadipocytes, GCs have pro-adipogenic effects through a GR-mediated increase in the expression of C/EBPB and PPARG2 transcription factors



Effects of GC on adipocytes. Inactive GC are activated through the action of the specific enzyme 11b-HSD1. GCs can then bind to their receptors (GC receptor, or GR) or to the mineralocorticoid receptor (MR). The overall action of GCs on mature adipocytes leads to an increase in lipolysis (augmented LIPE, ATGL, and MGLL), a decrease in glucose uptake (decreased GLUT1 and GLUT4) and insulin resistance (reduced IRS1).

2- β-adrenergic receptor antagonists

β-adrenergic receptor antagonists βARAs antagonize the effect of catecholamines at β-adrenoceptors, they are used to treat a broad spectrum of illnesses.

Cardiovascular applications include (hypertension, angina pectoris , tachydysrhythmias)

Noncardiovascular uses include ;

(treatment of essential tremor, pheochromocytoma, glaucoma, anxiety and migraine headaches)

there are at least three β-receptor subtypes ;

1-the β1 subunit, located in myocardium, kidney, and eye

2-the β2 subunit, found in adipose, pancreas, liver, and muscle tissue

3-the β3 subunit, located in adipose tissue

♦ Stimulation of the β1 subunit produces increased chronotropy and inotropy in the heart, as well as increased renin secretion by the kidney and aqueous humor production in the anterior chamber of the eye. Beta2 ,agonism relaxes smooth muscle in blood vessels and the bronchial tree intestinal tract, and uterus. Additionally, β2 activation prepares the body for increased metabolic demands during periods of stress by stimulating lipolysis and glycogenolysis and stimulate insulin secretion from pancreas. The β3 subunit may alter lipid metabolism by induction of .lipolysis

Beta blockers effect

beta-adrenergic stimulation enhances insulin and glucagon secretion, as well as glycogenolysis, gluconeogenesis, and lipolysis. alpha-adrenergic stimulation inhibits insulin secretion and may inhibit glucagon secretion and enhance liver glycogenolysis. In nondiabetics, beta-blockers represent minimal risk of affecting glucose control. In insulin-dependent diabetics, beta-blockers can prolong, enhance, or alter the symptoms of hypoglycemia, while hyperglycemia appears to be the major risk in noninsulin-dependent diabetics. beta-blockers can potentially increase blood glucose concentrations and antagonize the action of oral hypoglycemic drugs

♫ Activation of the sympathetic nervous system (SNS) has been linked to hypertension. Beta-blockers, which decrease SNS activation via beta-adrenergic receptor antagonism, are effective in lowering blood pressure and reducing cardiovascular morbidity and mortality in several conditions, including post-myocardial infarction and heart failure. Despite these clinical benefits, many physicians are reluctant to prescribe beta-blockers because of perceived negative metabolic effects, including reduced glycemic control, masking of hypoglycemia, insulin resistance, and dyslipidemia

Beta-adrenergic (β-AR) receptor blockers (BBs) are an essential class of drugs as they have numerous indications. On the other hand, they have numerous unwanted effects which decrease the compliance, adherence, and persistence of this very useful group of drugs. Stress–induced hypercatecholaminemia acts on β-AR of cardiomyocytes; it increases heart rate and contractility, effects suppressed by BBs. The answers of the organism to hypoglycemia and hypotension share the main mechanisms such as sympathetic nervous system activation and hypercatecholaminemia. Thus, there is a striking analogy: BBs can cover up symptoms of both hypoglycemia (which is widely known) and of hypotension (which is not recognized). It is widely known that BBs can cause hypotension. However, they can also complicate recovery by spoiling the defense mechanisms in hypotension as they interfere with the crucial compensatory reflex to increase blood pressure in hypotension

♦ Beta blockers consist of nonvasodilating and vasodilating agents, which . differ in terms of their mechanisms of action and effects on glucose and lipid metabolism. Treatment with nonvasodilating beta blockers is associated with an increased propensity of patients with hypertension to develop diabetes. A study demonstrated that patients treated with nonvasodilating beta blockers had a 28% higher risk of developing diabetes than patients on no .pharmacologic treatment for hypertension

nonvasodilating beta-blockers are associated with a worsening of glycemic , .and lipidic control

Nonvasodilating beta blockers (atenolol, metoprolol, pindolol, and propranolol) reduce blood pressure in association with a cardiac output reduction and may increase or have no appreciable influence on peripheral vascular resistance.

Nonvasodilating beta blockers include first- and second-generation agents. First-generation beta blockers (propranolol) block both beta1- and beta2-adrenergic receptors (nonselective beta blockade), whereas second- generation beta blockers (atenolol and metoprolol) specifically target beta-adrenergic receptors (cardioselective beta blockade). Nonvasodilating beta blockers significantly decrease insulin sensitivity by approximately 14% to 33% among patients with hypertension However, glucose levels at a particular timepoint may not reflect long-term changes in glucose metabolism as reflected by hemoglobin Alc (HbA1c). As an example, after 6 months of treatment, once-daily metoprolol did not affect fasting plasma glucose but significantly increased HbA1c levels by a relative increase of 5% from baseline in patients with hypertension

.

♫ Although the specific mechanisms have not been identified, several have been postulated to explain the negative effects of nonvasodilating beta blockers on glucose and lipid metabolism, most of which relate to their hemodynamic effects. Treatment with nonvasodilating beta blockers, which block either the beta-adrenergic receptor or the beta1- and beta2-adrenergic receptors, results in unopposed alpha-adrenergic receptor activity (which can induce vasoconstriction), decreased blood flow to the muscles, and reduced insulin-stimulated glucose uptake in the periphery

Nonvasodilating beta blockers may also interfere with with insulin secretion from pancreatic beta cells. Moreover, beta blockers may decrease the first phase of insulin secretion (potentially an important predictor of diabetes) via impairment of beta-mediated insulin release. Weight gain also has been noted in patients who received nonvasodilating beta blockers and is closely linked to an increased risk for developing diabetes

Vasoconstricting (diabetics friendly beta blockers because of their alpha blocking activity) beta-blocker use is associated with a reduction in HDL cholesterol, higher triglyceride, total cholesterol and LDL cholesterol levels, whereas carvedilol, a vasodilating beta-blocker, has not been associated with .these effects

In contrast, vasodilating beta-blockers (carvedilol, labetalol, and nebivolol) reduce peripheral vascular resistance but have little or no effect on cardiac output. Numerous studies have established that vasodilating beta-blockers are associated with more favorable effects on glucose and lipid profiles than -nonvasodilating beta

blockers

Improvements in glucose and lipid metabolism mediated by vasodilating beta-blockers may help reduce coronary artery disease risk among high-risk patients with

hypertension

Bisoprolol, a beta1- selective adrenergic blocker, was reported to have a neutral effect on glucose and insulin levels during a glucose tolerance test after .24 weeks of treatment at 5 to 10 mg/day in 13 patients with hypertension

Increased peripheral blood flow from the action of vasodilating beta blockers . may result in efficient glucose dispersal to the skeletal muscles, thereby facilitating insulin sensitivity. The mechanisms responsible for the beneficial effects of vasodilating beta blockers on glucose and lipid metabolism are not entirely understood but may include alpha-adrenergic receptor blockade, vasodilation, reduced oxidative stress, anti-inflammatory activity, and lack of weight gain

(beta-blockers with alpha-blocking properties (e.g. carvedilol

may have a reduced or no risk for diabetes . This discrepancy

has been attributed to differences in effects on insulin sensitivity

compared to conventional beta-blockers. These findings warrant

consideration of a beta-blocker with vasodilating properties, such

as carvedilol and nebivolol, as the preferred choice for persons

with diabetes or those at high risk for diabetes

A large clinical trial that compared the metabolic effects of metoprolol (a selective inhibitor of β1 recep- tors) to carvedilol (which inhibits β1, β2, and α1 recep- tors), carvedilol demonstrated more favorable effects on glycemic control and fewer hypoglycemia symptoms

a study confirms previous findings of a reduction in insulin sensitivity after chronic metoprolol treatment. Carvedilol treatment, however, resulted in a small amelioration of insulin resistance and a better lipid profile . We thus demonstrate that a beta-blocker with alpha 1-blocking properties has favorable effects on glucose metabolism, suggesting a potentially important role of peripheral blood flow in regulating glucose uptake. These findings imply that beta-blocker treatment, when combined with alpha 1-blocking activity has advantageous effects on insulin sensitivity and lipids and could therefore be suitable for patients with the metabolic syndrome

In patients with type 2 diabetes currently receiving a renin-angiotensin blocker, compared with metoprolol tartrate, the addition of carvedilol for blood pressure control resulted in a significant decrease in triglyceride, total cholesterol and non-HDL cholesterol levels. The use of metoprolol resulted in a significantly greater rate of initiation of statin therapy or an increase in the dose of existing statin therapy when compared with carvedilol utilization

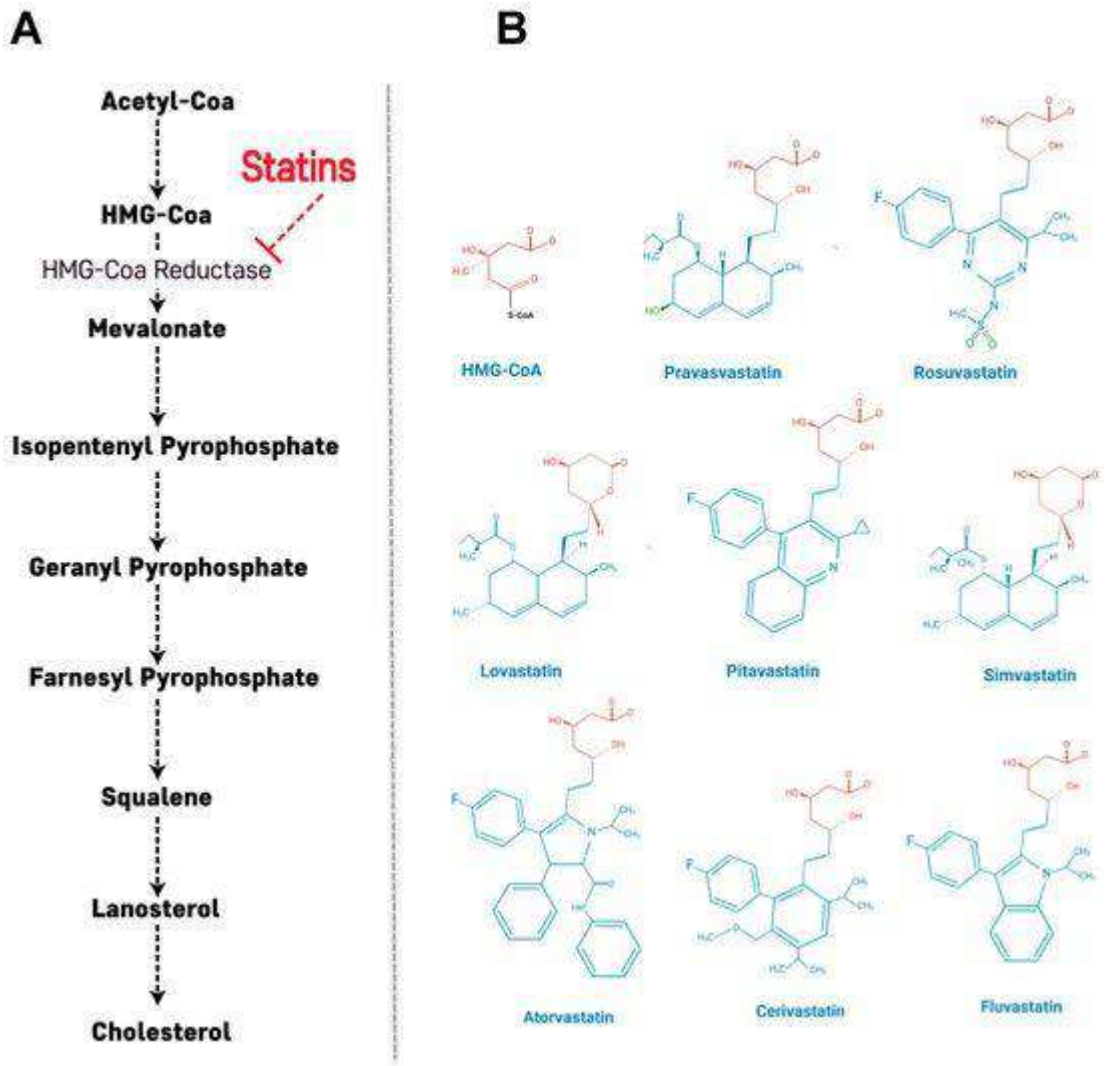
3- Statins

♦Primary Action of Statins: Cholesterol Biosynthetic Pathway

Statins are reversible and competitive inhibitors of HMG-CoA reductase, which is the rate-determining enzyme in the cholesterol biosynthetic pathway . The HMG-like portion of statins which is a modified 3,5-dihydroxyglutaric acid moiety, is structurally similar to HMG-CoA and causes the inhibition of HMG-CoA reduction reactions . Through this mechanism, the mevalonate pathway is inhibited along with a consequent decrease in downstream products and cholesterol synthesis . In addition, this statin-mediated decrease in intracellular cholesterol content leads to up-regulation of the LDL receptor (LDLR) in the

liver and peripheral tissues, resulting in decreased blood LDL cholesterol (LDL-C) . LDLR is the primary route by which LDL-C is removed from circulation, and its synthesis has been shown to be inversely correlated to the amount of cholesterol synthesized by a cell . Through the action of statins, the cellular cholesterol concentration decreases, stimulating production of more LDLR and promoting LDL-C removal from the bloodstream, ultimately reducing CVD risk

Statins are classified according to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin and simvastatin) . The solubility and pharmacological properties of statins are determined by the substituents on the ring attached to the active moiety . Hydrophilicity originates from polar substituents added to the active site while the addition of nonpolar substituents leads to lipophilicity . Although the target of both types of statins is HMG-CoA reductase the inhibitory mechanisms are distinct. Hydrophilic statins target the liver more efficiently because their uptake is carrier-mediated, while lipophilic statins passively diffuse through the hepatocellular membrane and similarly are also able to diffuse in extrahepatic tissues, thus showing reduced hepatoselectivity . Their diffuse influence on extrahepatic tissues may explain the higher incidence of adverse effects observed with lipophilic statins. The notable exception to this is rosuvastatin which is a ,hydrophilic statin but has a similar activity profile to lipophilic statins.



♦Beneficial Effects of Statins on Diabetic Complication and/or Inflammation in T2DM

There are many factors that contribute to the development of atherosclerotic cardiovascular disease, the main mortality cause in T2DM patients. These include dyslipidemia, increased oxidative stress, enhanced protein glycation or chronic inflammatory state all of them worsen in T2DM . Statins are the gold standard treatment for the prevention and management of cardiovascular disease and their use in T2DM patients is recommended by The American Diabetes Association 2019 guidelines . In addition to the reduction of cholesterol levels and dyslipidemia improvement by reducing lipoprotein levels in plasma, the pleiotropic effects of statins reduce high sensitive C-reactive protein and other pro-inflammatory markers , improve endothelial function and reduce oxidative stress , which together contribute to a significant CVD

reduction in T2DM patients. Several clinical trials have pointed out the beneficial effects of statins in diabetic patients . The collaborative atorvastatin diabetes study (CARDS) showed nearly 40% reduction in relative risk of cardiovascular events in diabetic patients aged 45-70 years old with high cholesterol levels and treated with atorvastatin during 4 years . A meta-analysis of 14 randomized trials including more than 18,000 patients confirmed the beneficial effects of statins in diabetic patients showing a 21% reduction in major vascular events per mmol/L LDL-C reduction . Further studies, confirmed the benefits of statin treatment in diabetic patients independently of LDL-C baseline . Unfortunately, in some cases, statin treatment leads to adverse effects such as the decreased insulin sensitivity shown by atorvastatin, simvastatin and rosuvastatin . For atorvastatin and simvastatin, one proposed explanation is that the higher diffusion rate of lipophilic statins to the intracellular space can interfere with cellular processes, leading to decreased intracellular insulin secretion in response to glucose . For rosuvastatin, despite its hydrophilicity, the higher affinity and efficient transport of rosuvastatin into cells, which can underlie it effects on insulin sensitivity

Statins are a guideline-directed, first line therapy for prevention of primary and secondary cardiovascular disease (CVD), which is the leading cause of mortality worldwide . Although the principal mechanism of the action of statins is inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase, statins have been implicated in several other beneficial pleiotropic effects including improving endothelial function, stabilization of atherosclerotic plaques and anti-inflammatory activities . Despite the safety and relative tolerability of statins, observational studies , clinical trials and meta-analyses have found that statins can increase the risk of new-onset type 2 diabetes mellitus (T2DM). These studies implicated statins in negatively impacting insulin sensitivity, decreasing secretion by pancreatic β-cells and increasing insulin resistance.while the lipid-lowering mechanism of statins is relatively well understood, the mechanisms underlying statin-induced T2DM development seem to be multifactorial and remain unclear. Among experimental studies, multiple works have indicated that statins diminish pancreaticβ-cell function via Ca2+ signaling pathways impairment , compromise insulin signaling and down-regulate the insulin-responsive glucose transporter 4 (GLUT-4) . In addition, it has also been described that statins

impact on epigenetics may also contribute to statin-induced T2DM via differential expression of microRNAs This review focuses on the evidence and mechanisms by which statin therapy is associated with the development of T2DM. Here, we will describe the existing data from clinical studies as well as experimental results that shed some light on the mechanisms of this association .

♦Proposed Mechanisms for T2DM Development Induced by Statins

Overall, the mechanisms by which statin treatment induces T2DM are not fully understood, but both on-target and off-target effects may be involved. Among these, inhibition of the mevalonate pathway results in a reduction in several cellular biosynthetic pathways including those involved in glucose homeostasis . Over time, chronic statin treatment increases gluconeogenesis by upregulating gene expression of key enzymes that increase glucose production in the liver. In addition, it has been shown that statins can impair the insulin signaling pathway as well as downregulate the GLUT-4 transporter, which is responsible for the uptake of glucose in peripheral cells . Statins can also induce changes in circulating free fatty acids (FFA), changes in hormones such as adiponectin and leptin impairment of β-cell function, β-cell cell damage and adipocyte maturation/differentiation . Additional mechanisms involving epigenetic regulation mediated by specific microRNAs have also being involved in the reduction of insulin secretion . These complex pathophysiologic ,molecular mechanisms of statin-induced T2DM; summarized in Fig(2)

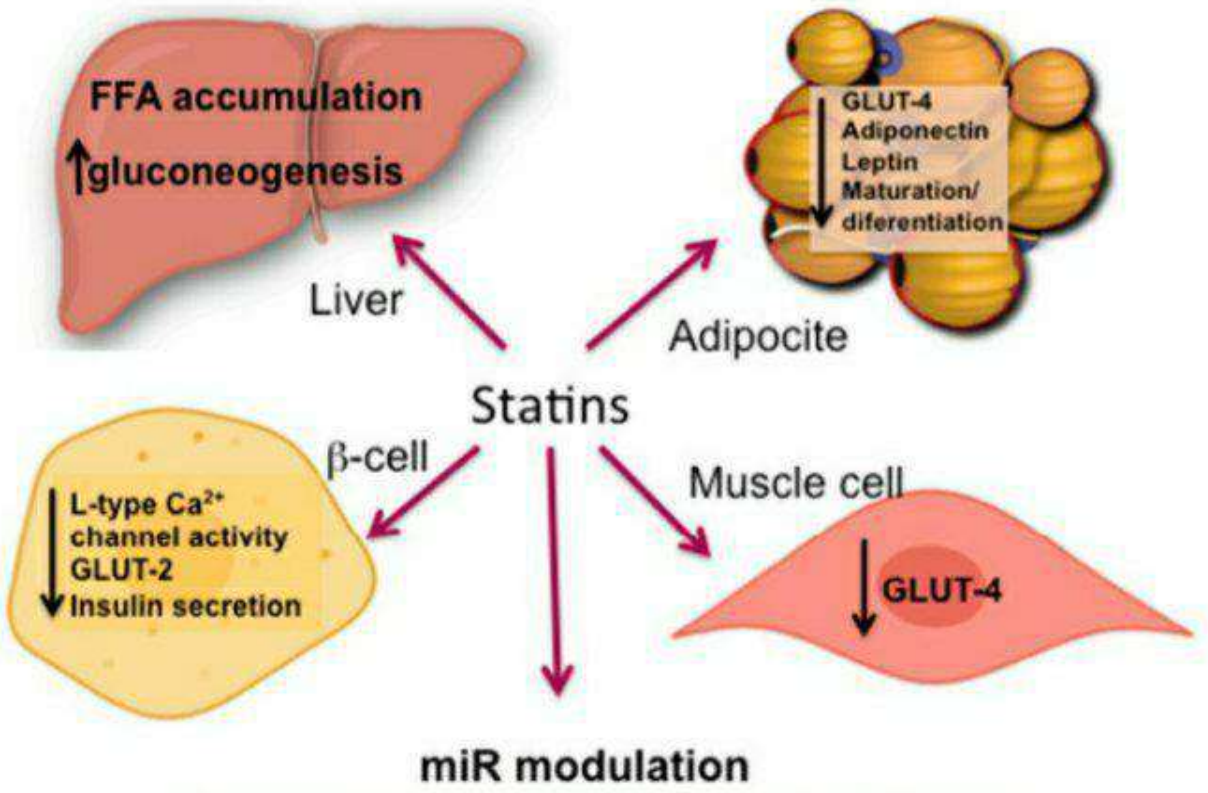


Figure 2. Principal mechanisms for T2DM development induced by statins.

1-Dysfunctional Effects Caused by Statins in Pancreatic B-Cell

Insulin secretion from pancreatic B-cells is initiated by glucose-induced Ca2+ entry controlled by voltage-gated Ca2+ channels . Therefore, maintenance of intracellular Ca2+ homeostasis is tightly regulated in order to ensure proper insulin secretion and maintain the integrity of the B-cell physiology . Briefly, glucose uptake activates glycolysis in B-cell thus elevating the [ATP]/[ADP] ratio. This acts as a signal that closes KATP channels and depolarizes the plasma membrane, with subsequent activation of voltage-dependent Ca2+ channels, entry of extracellular Ca2+ and finally insulin exocytosis . ATP sensitivity of the

KATP channels is modulated by several effectors including PIP and acyl CoAs . Conversely, a decrease in the metabolic signal causes reopening of KATP channels and suppresses the electrical trigger for insulin secretion, thereby providing feedback regulation of insulin secretion . In addition, ATP and ADP can act as autocrine activators of B-cell purinergic receptors because they are also within insulin exocytosis granules . Indeed, inhibition of both P2X and P2Y purinergic receptors causes a reduction in glucose-induced insulin secretion

To date, the relationship between statin-mediated inhibition of cholesterol synthesis and impaired L-type Ca2+ channel activity remains unclear. However, in vitro studies have indicated that simvastatin can directly inhibit L-type Ca2+ channels in rat pancreatic islet B-cells. Specifically, because simvastatin was found to immediately inhibit channel activity, it has been suggested that there is a direct interaction between simvastatin and the channel. In contrast, pravastatin lacks L-type Ca channels inhibition, possibly because of its lipophilicity . Alternatively, other authors have suggested that the long-term cholesterol reduction caused by statins can lead to incorrect sorting of membrane lipid-raft bound proteins or conformational changes of the Ca channel subunits More recently, it has been suggested that statins can reduce the membrane potential by inhibiting mitochondrial complex II activity, which causes oxidative stress . These off-target effects of statins have been very recently corroborated by Curry et al. in experiments showing that simvastatin impairs B-cell function by at least two mechanisms:

(1) via direct inhibition of KATP channels in a mitochondria-independent manner

(2) via interference with mitochondrial respiration, thus

decreasing cytosolic ATP levels and inhibiting metabolic upregulation of L-type Ca2+ channels. As described before, insulin is secreted by B-cells in response to glucose uptake through GLUT receptors (primarily GLUT-1 to 4), with GLUT-2 being the predominant isoform in B-cells . GLUT-2 represents a high-affinity and low-capacity glucose transporter. It has been shown that treatment of B-cells with atorvastatin and pravastatin inhibited GLUT-2 expression in a

concentration-dependent manner. However, rosuvastatin and pitavastatin showed a slight increase in GLUT-2 expression . In addition to this, it has also

been observed in mouse pancreatic B-cell line MIN6 cells that simvastatin treatment diminishes GLUT-2 mRNA and protein expression via a dose-dependent reduction of ATP production . Another mechanism through which statins may interfere with glucose metabolism is the statin-mediated LDLR upregulation that increases cholesterol uptake in the B-cell leading to reduced mRNA and protein expression of GLUT-2, consequently limiting glucose uptake . The direct inhibition of the mevalonate pathway by statins reduces the intracellular concentration of isoprenoids, the final products of the pathway. Isoprenoids are essential for G protein posttranslational modification, which is important for insulin granule exocytosis . Interestingly, it has been shown that the glucose-induced insulin secretion by lovastatin in normal rat islets is reduced by co-incubation with mevalonate . The adverse effects of statins are summarized in Fig(3)

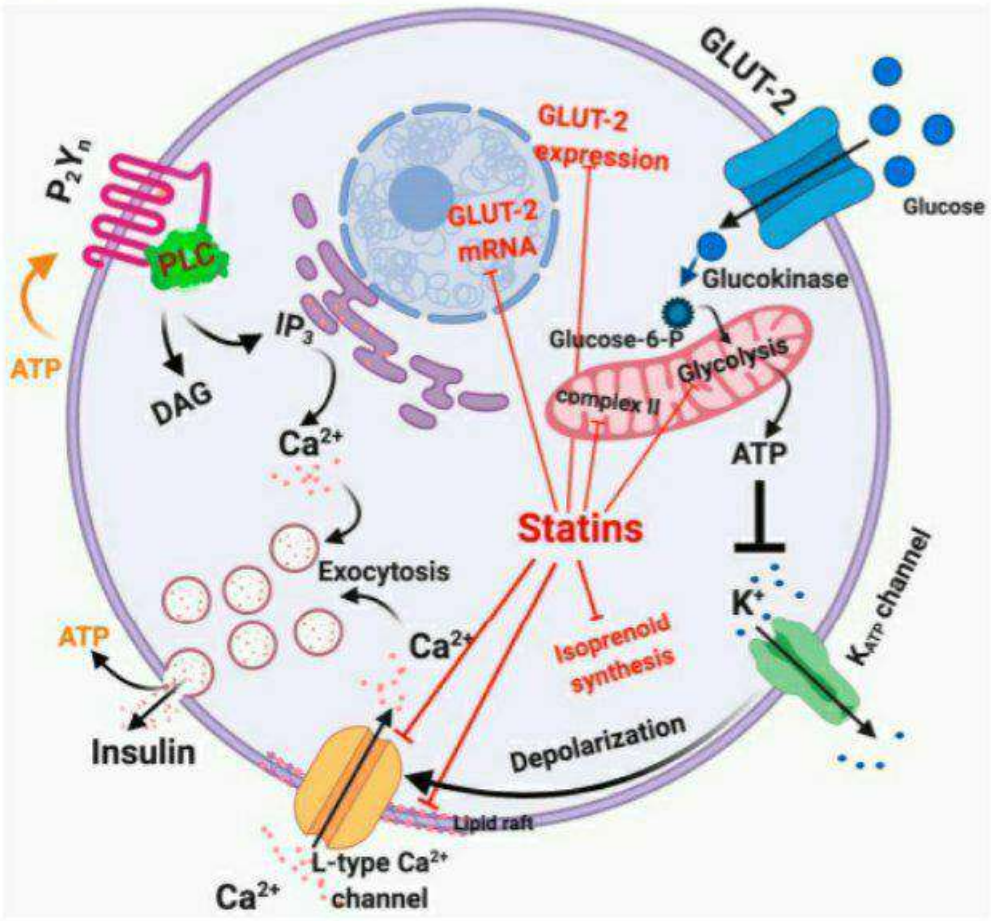


Figure 3. Intracellular actions of statins in β-cells. Red lines indicate the mechanisms affected by statins.

2-statin Induced IR

The binding of insulin to the insulin receptor (INSR) triggers insulin signaling with the physiologic objective of normalizing high blood glucose levels . Insulin binding induces structural rearrangements in the INSR leading to auto-phosphorylation of tyrosine residues. The downstream events that follow INSR activation include recruitment of several adaptor proteins, facilitating a suitable binding site for insulin receptor substrates (IRS) that once phosphorylated, trigger several downstream signals . Among them, IRS-1 is phosphorylated and activates different kinases such as Akt, PKC, SIK2, S6K1, mTOR, ERK1/2 and ROCKI . IRS-1 activates PI3K, which in turn, catalyzes the conversion of PIP2 to PIP's, which activates Akt, among other targets [85]. Akt activation leads to glucose uptake by facilitating GLUT-4 translocation to the plasma membrane . GLUT-4 is an insulin-dependent glucose transporter primarily expressed in adipose tissue, cardiomyocytes and skeletal muscle cells

2.1-Adipose Tissue

Recently, evidence that statin treatment impairs the insulin signal transduction process in adipocytes, including INSR, GLUT-4, Akt, some small GTP-binding proteins (G-proteins) and caveolae integrity has been demonstrated. Multiple studies have shown that atorvastatin and lovastatin reduce GLUT-4 expression at the plasma membrane in 3T3L1 adipocytes and a similar effect has been described with atorvastatin in mouse-white adipose tissue, thus impairing glucose tolerance . The statin-induced decrease in GLUT-4 translocation to the plasma membrane has been attributed to inhibition of isoprenoid synthesis . In fact, isoprenylation is essential for the correct functioning of several proteins involved in the GLUT-4 translocation process. As previously described,

isoprenylation is impaired due to statin-induced inhibition of the mevalonate pathway. In one illustrative example, it has been described that atorvastatin disrupts plasma membrane colocalization of Rab-4 and RhoA through inhibition of geranylgeranyl pyrophosphate synthesis. Rab-4 and RhoA are isoprenoid-dependent proteins, which are involved in the insulin-induced translocation of

GLUT-4, thus their atorvastatin-mediated dysfunction may disturb overall insulin signaling

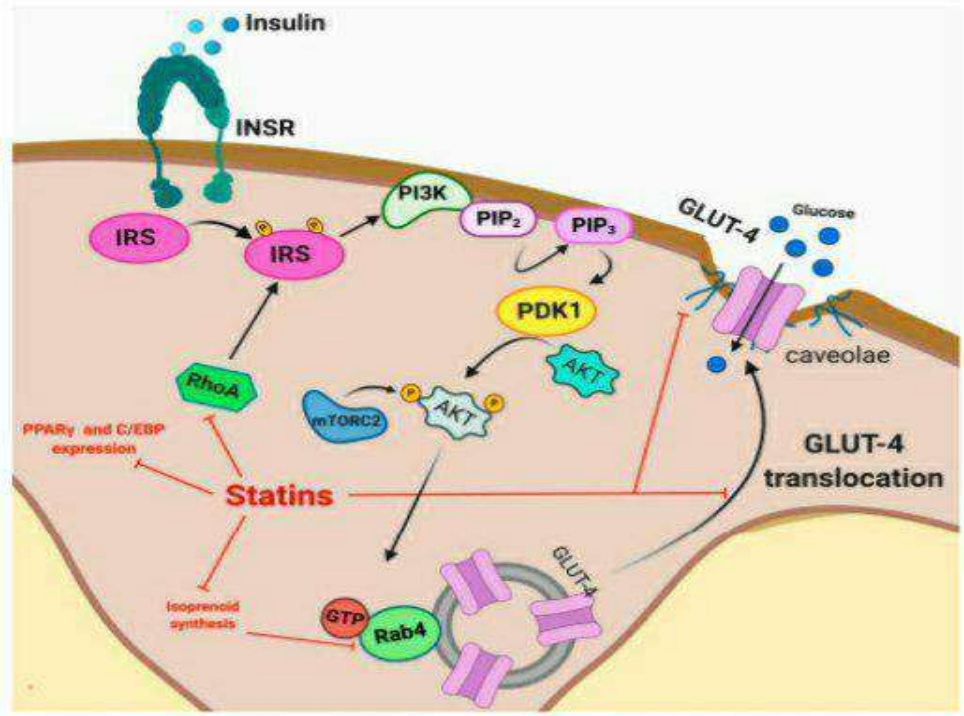


Figure 4. Intracellular actions of statins in adipocytes. Red lines indicate the mechanisms affected by statins.

2.2-Skeletal Muscle

Skeletal muscle is the major tissue consuming most of the glucose that enters circulation , and any impairment in glucose uptake by this tissue may result in T2DM development. GLUT-4 mediates glucose transport into skeletal muscle cells, representing a key factor for blood sugar control As indicated above, insulin binding to INSR causes Akt activation and translocation of GLUT-4 containing vesicles to the plasma membrane, thus facilitating the transport of glucose . Although the mechanism of statin induced T2DM is not completely understood, there are both in vivo and in vitro studies that shed some light on this phenomenon in skeletal muscle. Some of the mechanisms that have been

previously described are statin-mediated inhibition of insulin stimulated glucose uptake, impairment of intracellular signaling of the INSR and thereby of the Akt/mTOR pathway, or an excess of FFA accumulation in skeletal muscle as . a consequence of HMG-CoA reductase inhibition.

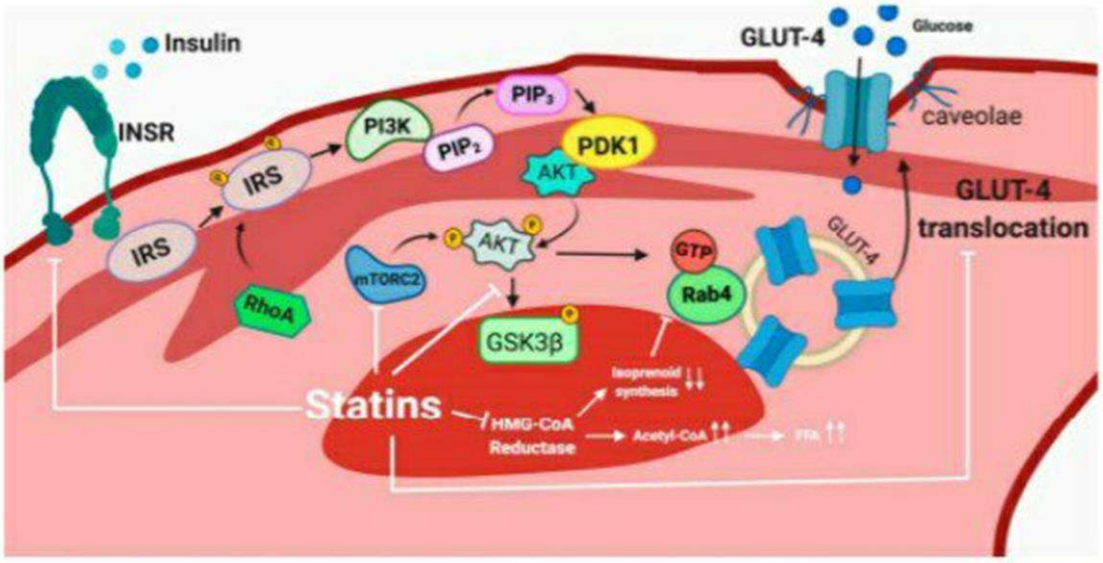


Figure 5. Intracellular actions of statins in muscle cells. White lines indicate the mechanisms affected by statins.

2.3-Liver

The liver plays a central role in glucose homeostasis and is exquisitely sensitive to insulin. In fact, insulin regulates many hepatic metabolic pathways ranging from the glucose output to lipid synthesis. Therefore, impairment of hepatic insulin sensitivity is rapidly reflected in glucose homeostasis and triglyceride levels. Emerging evidence has demonstrated that statin treatment is associated with worsening glycemic control in the liver .Several mechanisms possibly involved with the effect of statins on glucose metabolism in the liver are summarized below. Statin therapy is associated with a small increment in fasting blood glucose levels. It has been shown that statins can stimulate endogenous glucose production by activation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) ,the major rate-limiting gluconeogenic enzymes in human liver cells. The elevation of hepatic

gluconeogenesis contributes to hyperglycemia, which is characteristic of insulin resistance and T2DM. Regarding FFAs, it has been shown that an excess of FFA accumulation in liver cells can contribute to the development of T2DM .Interestingly, atorvastatin and rosuvastatin treatment upregulates thyroid hormone-responsive spot 14 protein (THRSP) expression, which is a small protein predominantly expressed in lipid-producing tissues such as those found in the liver THRSP has been implicated as a regulator of the lipogenic processes by controlling the expression of lipogenic genes such as fatty-acid synthase .(FASN), ATP citrate lyase (ACLY) SREBP and ChREBP or their activity .

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predominantly expressed in lipid-producing tissues such as those found in the liver. THRSP has been implicated as a regulator of the lipogenic processes by controlling the expression of lipogenic genes such as fatty-acid synthase (FASN), ATP citrate lyase (ACLY) SREBP and ChREBP or their activity ,The .adverse effects of statins in the hepatocytes are summarized in Figure

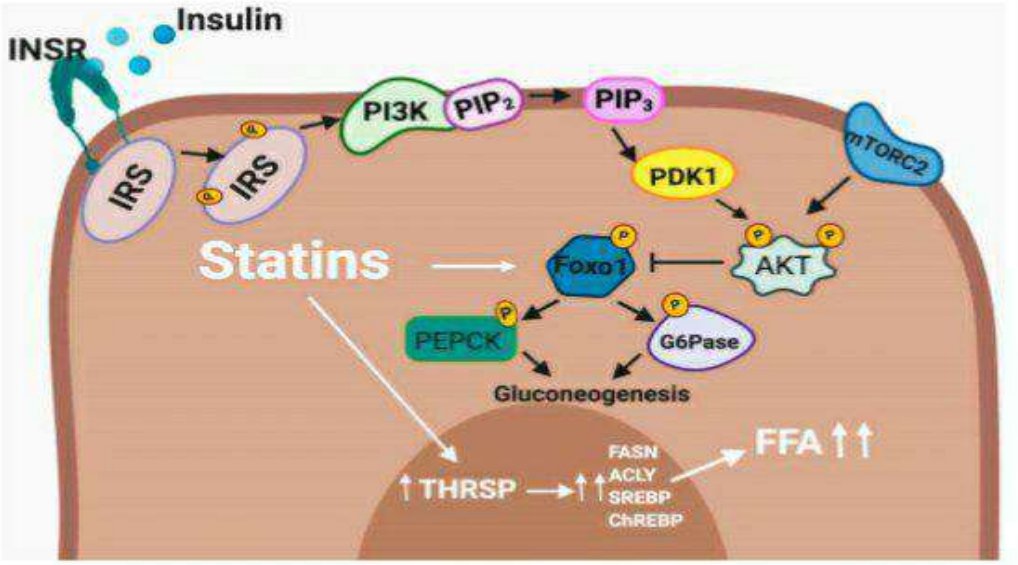


Figure 6. Intracellular actions of statins in hepatocytes. White lines indicate the mechanisms affected by statins.

3-MicroRNAs and Impact of Statin Therapy on microRNA Expression Profile

MicroRNAs (miRs) are small (22 nucleotide) noncoding regulatory RNAs, which act as post-transcriptional regulators of gene expression . miRs usually silence gene expression through mRNA degradation or sequestration of the target mRNA from translation machinery through mRNA degradation or sequestration of the target mRNA from translation machinery]. It has been shown that miRs are involved in many biological processes including insulin expression skeletal muscle adaptation to elevated glucose, insulin sensitivity and glucose stimulated insulin secretion (GSIS) . It has been shown that miRs likely mediate the pleiotropic effects of statins via modulation of lipid metabolism, enhancement of endothelial function, inhibition of inflammation improvement of plaque stability and immune regulation. More specifically, miRs appear to regulate the fine-tuning of cellular phenotypes rather than serving as .molecular on–off switches

Statin therapy has been found to affect the expression of several miRs, which play a central role in the regulation of lipid and glucose metabolism and that are associated with development of T2DM

3.1- miR Modulation of Cholesterol and Lipid Homeostasis

3.2- Modulation of Hepatic Glucose Production

3.3- Modulation of the Insulin Signaling Pathway

Differences in Diabetogenic Effects between Hydrophilic and Lipophilic Statins

As indicated in previous sections, lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin) may be more diabetogenic than hydrophilic statins (pravastatin and rosuvastatin) as they can more readily penetrate extrahepatic cell membranes such as β-cells, adipocytes and skeletal muscle cells. Conversely, hydrophilic statins (e.g., pravastatin) are more hepatocyte specific and less likely to enter β-cells or adipocytes . Indeed, a high hepato-selectivity translates into minimal interference with cholesterol metabolism in tissues other than the liver and consequently to a lesser diabetogenicity .Several studies have shown that the detrimental effects of statins are dose and potency dependent and primarily related to their lipophilicity. While lipophilic statins have negative effects on pancreatic β-cell function, for hydrophilic statins such as pravastatin, neutral or improving effects have been observed . , it has been reported that statins can inhibit glucose-induced cytosolic Ca2+ signaling and insulin secretion by blocking L-type Ca2+ channels in β-cells. These inhibitory potencies may be particularly evident for the lipophilic rather than the hydrophilic statins. Indeed unlike hydrophilic statins, the lipophilic ones have a strong affinity for the cell membrane, and therefore have easier access to the intracellular space . In this ,,context, statins may inhibit the endogenous

metabolic pathways described that they are associated with glucose-stimulated insulin secretion, including endogenous cholesterol synthesis and Ca2+-dependent insulin responses to glucose . It has been shown that atorvastatin (lipophilic) but not pravastatin (hydrophilic affects insulin release and (mitochondrial metabolism due to the suppression of antioxidant defense

.system and induction of ROS production in pancreatic β-cell models

GLUT-4 mediates insulin-stimulated glucose uptakein a

process that requires fusion of the transporter with the plasma membranes facilitated by IRS-1 and several kinases .The small GTP-binding proteins are also key players in this process and they require isoprenylation by mevalonate products for their association with the cell membranes. The statin-mediated inhibition of the synthesis of the above products increases insulin resistance

in parallel with the mevalonate synthesis inhibitory capacity . Furthermore, several other processes involved in the GLUT-4 signaling pathway may be inhibited by statins. These include IRS-1 insulin receptor β subunit, and Akt phosphorylation.It has been suggested that these effects are relevant only for ,lipophilic statins (e.g., atorvastatin and simvastatin), but not for hydrophilic

statins (e.g., pravastatin) . The capacity of the former to enter adipocytes through passive diffusion can help explain this difference.

4- Antipsychotic

Antipsychotic drugs (APDs) are widely prescribed to control schizophrenia and bipolar disorders, as well as other mental disorders including dementia, major depression, and even drug addiction . Typical APDs (also called first generation APDs) such as chlorpromazine, perphenazine and haloperidol were introduced to clinics more than 60 years ago. Therapeutic effects of typical APDs are mediated largely through potent blockage of dopamine D2 receptors, which also cause extra-pyramidal symptoms (EPS) side-effects . Since the 1990s, a number of atypical APDs (also called 2nd generation APDs) including olanzapine, clozapine and risperidone have been approved by the FDA, and are now widely used as first line APDs due to their improved tolerability and reduced EPS compared with typical APDs. In addition, clozapine has better outcomes in treatment- resistant schizophrenia. Besides blockage of D2 receptors, atypical APDs target multiple neuroreceptors such as serotoninergic 5-HT2A/5- HT2C, histaminergic HI and muscarinic M3 receptors . Although typical APDs have been reported causing a certain degree of metabolic disorders, atypical APDs, particularly clozapine and olanzapine, can cause much worse metabolic side- effects including body weight gain, obesity, hyperlipidaemia, insulin resistance, hyperglycaemia and diabetes . Since

psychiatric patients often face chronic and even life-time APD treatment, these side-effects are major considerations in APD medication . Schizophrenia patients with APD treatment have 2.5 times higher risk of developing type 2 diabetes according to a recent meta-analysis which examined 25 studies, including 145,718 individuals with schizophrenia and 4,343,407 controls. It is noteworthy that over the last decade APD prescriptions in children and adolescents have sharply increased . Recent studies have shown that APDs cause not only greater weight gain in children/adolescents than in adults but also significant risk of type 2 diabetes, which has been largely underestimated . These severe side-effects have a devastating impact on life quality, and is a key risk for severe health complications, including cardiovascular disease, stroke, and premature death . Understanding how diabetes develops in patients treated with APDs and preventing APD-induced diabetes will improve medication compliance.

Antipsychotic drugs (APDs) are widely prescribed to control various mental disorders. As mental disorders are chronic diseases, these drugs are often used over a life-time. However, APDs can cause serious glucometabolic side-effects including type 2 diabetes and hyperglycaemic emergency, leading to medication non-compliance. At present, there is no effective approach to overcome these side-effects. Understanding the mechanisms for APD-induced diabetes should be helpful in prevention and treatment of these side-effects of APDS and thus improve the clinical outcomes of APDs. In this review, the potential mechanisms for APD-induced diabetes are summarized so that novel approaches can be considered to relieve APD-induced diabetes. APD-induced :diabetes could be mediated by multiple mechanisms

1- APDs can inhibit the insulin signaling pathway in the target cells such as ;muscle cells, hepatocytes and adipocytes to cause insulin resistance

2- APD-induced obesity can result in high levels of free fatty acids (FFA) and .inflammation, which can also cause insulin resistance

3- APDs can cause direct damage to B-cells, leading to dysfunction and apoptosis of B-cells.

A recent theory considers that both B-cell damage and insulin resistance are necessary factors for the development of diabetes. In high-fat diet-induced diabetes, the compensatory ability of B-cells is gradually damaged, while APDS cause direct B-cell damage, accounting for the severe form of APD-induced diabetes. Based on these mechanisms, effective prevention of APD-induced diabetes may need an integrated approach to combat various effects of APDs .on multiple pathways

♣MECHANISMS FOR ANTIPSYCHOTIC-INDUCED DIABETES

Over the past 10 years, a number of studies have aimed to explore the potential mechanisms underlying APD-induced diabetes. Based on recent progress, we summarized the findings into three molecular mechanisms for explaining APD-induced diabetes:

(1)- insulin resistance due to the direct effect of APDs,

(2)- APD- caused insulin resistance through obesity, and

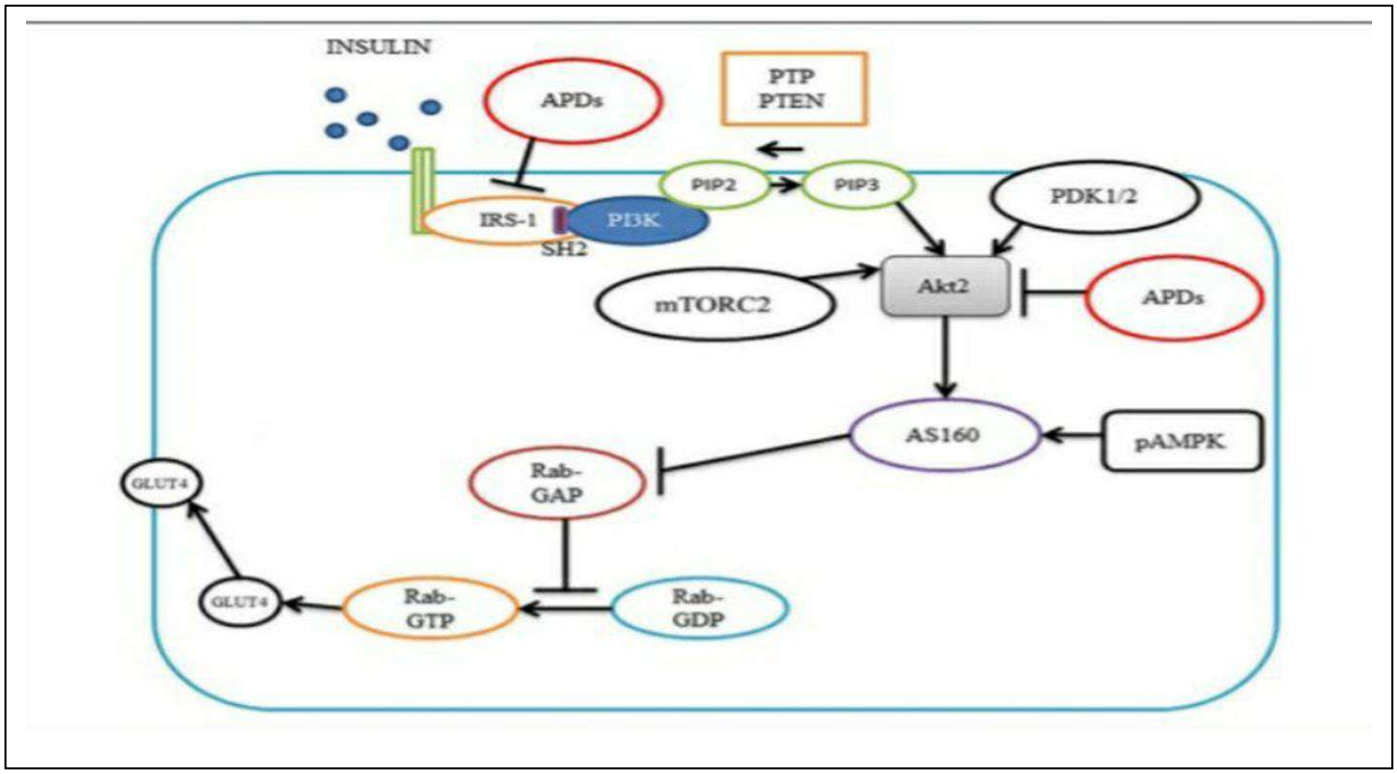
(3)- APD-induced B-cell dysfunction and apoptosis

Mechanism 1: Insulin Resistance Due to Direct Effect of Antipsychotics

Insulin, secreted by pancreatic B-cells, is the key hormone in promotion of glucose metabolism .It increases the uptake of glucose by cells and thus maintains the homeostasis of blood glucose levels. Insulin resistance refers to the situation where the target cells lose response to insulin stimulation and thus reduce glucose uptake .Increased blood glucose level are mainly caused by insulin resistance in the skeletal muscles, and also in the hepatic, renal and adipose tissue .Of these, the main site for glucose utilization is muscle tissue, and represents ~80% of glucose consumption

APD-induced insulin resistance could be independent of weight gain and increased food intake. It has been reported that, in patients within 3 months

after initiation or switch to atypical APDs, new-onset gluco-metabolic abnormalities and diabetes was not associated with weight change and BMI .A recent study has shown that a single administration of olanzapine caused glucose metabolism change independent of obesity in healthy human subjects .Aripiprazole has been shown to induce insulin resistance with metabolic changes where there is no weight gain or increase in food intake



Insulin signaling pathways and antipsychotic effects. Insulin binds to insulin receptors to activate IRS1, leading to activation of PI3K, which converts PIP2

into PIP3, PIP3 brings Akt2 on to the membrane where PDK1/2 and mTORC2 phosphorylate Akt2. Akt2 activates AS160, which blocks Rab-GAP, leading to

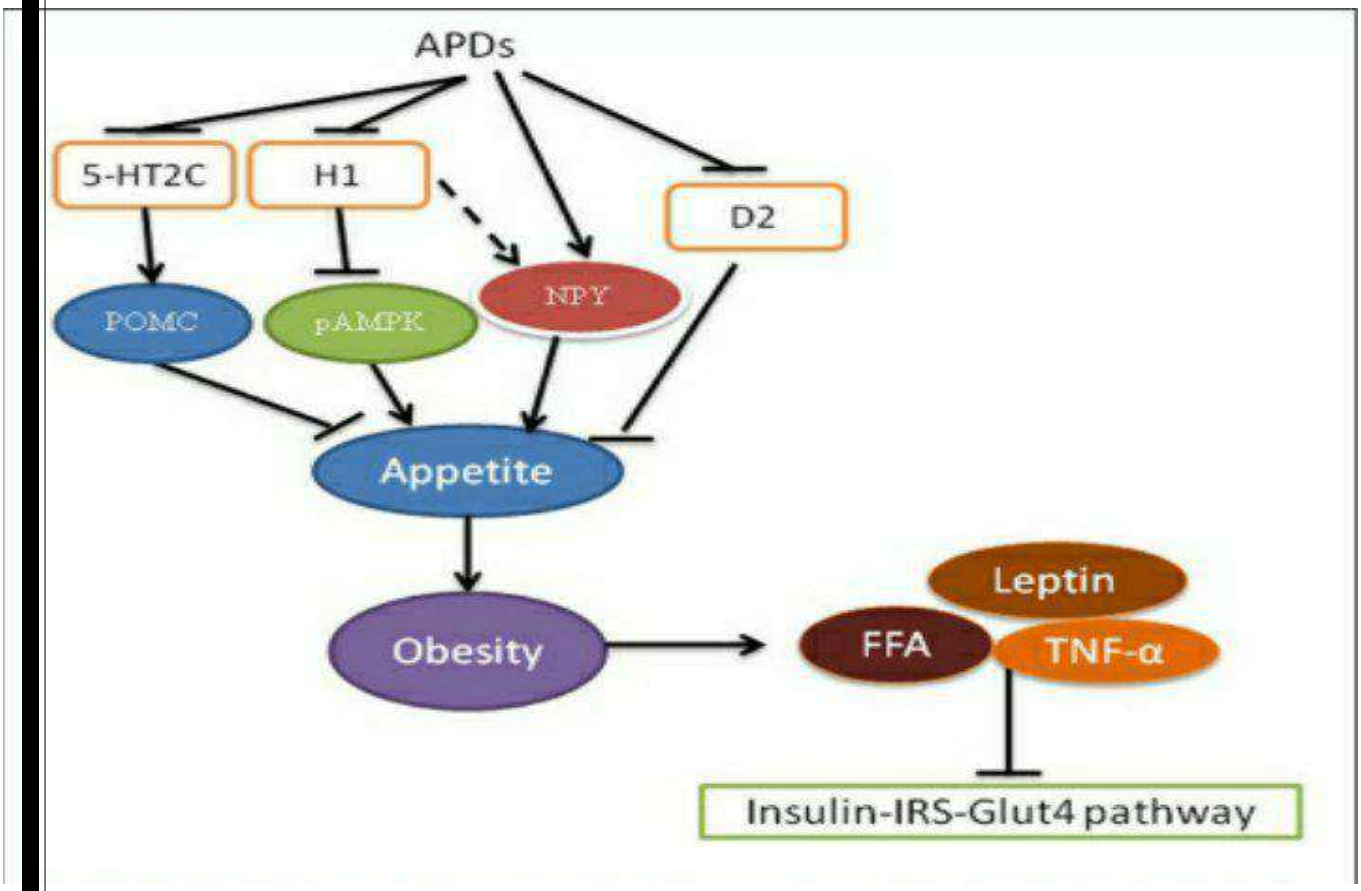
increased Rab-GTP, causing translocation of GLUT4 to the membrane for glucose transportation. Antipsychotics can diminish insulin-induced IRS-1 phosphorylation

and inhibit Akt activity causing insulin resistance. Akt2, protein kinase 2; pAMPK, phosphor-AMP-activated protein kinase; APDs, antipsychotic drugs; GLUT4; glucose transporter type 4; IRS1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol (3,4)-bisphosphate; PIP3,

phosphatidylinositol (3,4,5)-trisphosphate; PDK1/2, phosphoinositide-dependent kinase-1; mTORC2 mammalian target of rapamycin complex 2 and SH2, Src homology 2.

Mechanism 2: Antipsychotic-Caused Insulin Resistance through obesity

Antipsychotics cause insulin resistance via obesity. Antipsychotics block receptors 5-HT2C, histamine H1 and D2 receptors resulting in a decrease in POMC and an increase in NPY production, leading to increased appetite. Increased food intake results in obesity, which is associated with ,insulin resistance via increased FFA, leptin and TNF-α. pAMPK phosphor-AMP-activated protein kinase; APDs, antipsychotic drugs; FFA, free ;fatty acids; D2, dopamine D2 receptor; 5-HT2C, Serotonin 5-HT2C receptor NPY, neuropeptide Y; POMC, proopiomelanocortin; TNF-α, tumor necrosis .factor alpha



Mechanism 3: Antipsychotic-Induced Beta Cell Dysfunction and Apoptosis

The effects of antipsychotics on β-cells. Antipsychotics can block

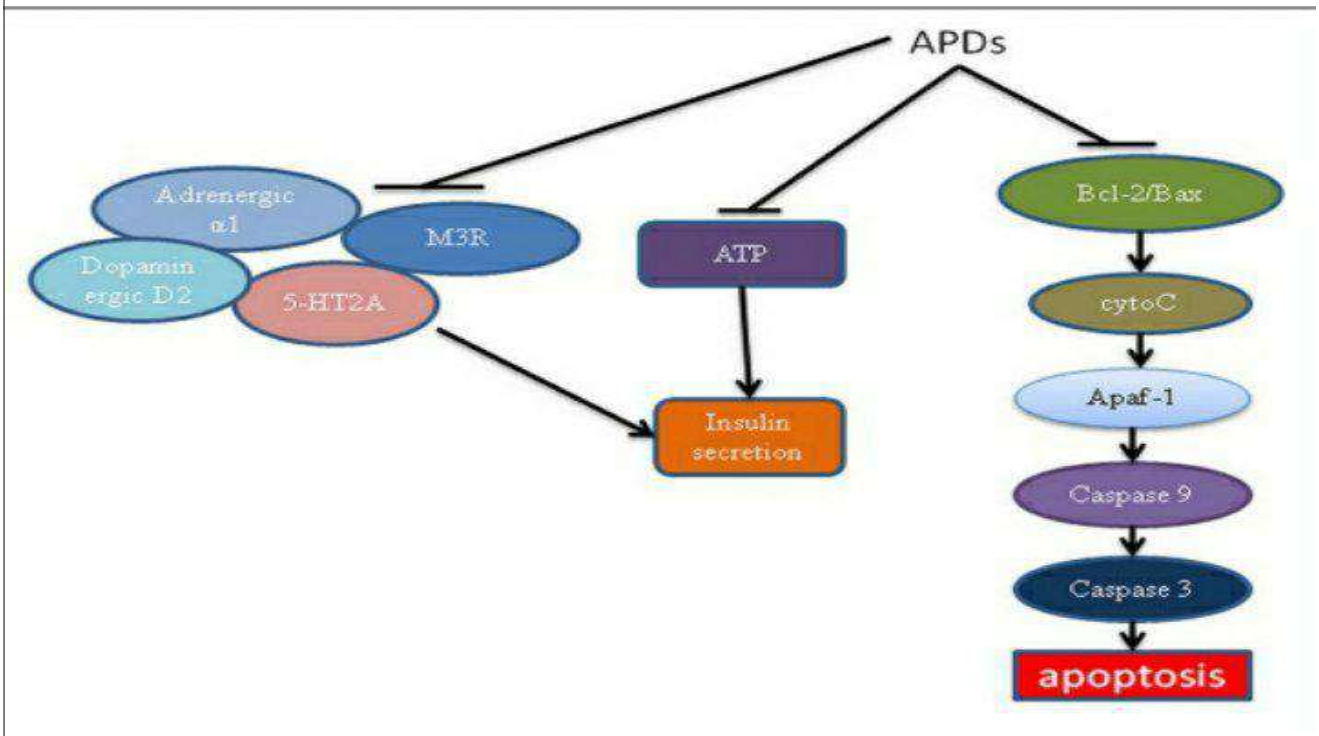
.ATP and M3, adrenergic α1 and 5-HT2A receptor-mediated insulin secretion

APDs act on the mitochondrial apoptotic pathway, leading to decreased Bcl-2

.ratio, increased cytochrome c release, Apaf/caspase activation and apoptosis

APDs, antipsychotic drugs; ATP, adenosine triphosphate; M3R, muscarinic M3

receptor; Apaf, apoptotic protease activating factor



5- Thiazide Diuretics

Thiazide diuretics are among the most commonly used antihypertensives. Significant adverse glycaemic events related to thiazide diuretics have been reported for more than 50 years .Side effects on glucose homeostasis have been described even at low doses of thiazides .Indeed, new-onset diabetes in

hypertensive patients was more frequent in those receiving low-dose diuretic therapy than in those receiving long acting nifedipine, with frequencies of 5.6 - ,versus 4.3% In a recent meta-analysis of antihypertensive trials

thiazides were associated with a higher risk of diabetes than placebo and, along with beta-blocking agents, they carried the highest risk among all major classes .of anti- hypertensives

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial,a compar- ison between groups of patients receiving chlorthalidone, amlodipine and lisinopril was conducted. The incidence of diabetes was significantly higher in the chlorthalidone group (11.6%) than in the other groups. However, and in spite of the risk of incident diabetes, thiazide diuretics do not seem to increase the risk of cardiovascular disease secondary to hyperglycaemia. This may be due, at least in part, to the effective reduction in blood pressure achieved by diuretic therapy

Mechanisms of diuretic-induced hyperglycaemia

seem to be related to a reduction in insulin secretion, secondary to diuretic-induced hypokalaemia. In fact, hypo- kalaemia is among the most important adverse effects of thiazide diuretics, and serum potassium levels decrease in a dose-dependent manner following thiazide treatment, so hyperglycaemia secondary to thiazide diuretics may be due, in part, to decreased insulin secretion secondary to potassium loss. Substitution with potassium salts can pre- vent deterioration in glucose tolerance and may restore Other jinsulin sensitivity, similarly to drug withdrawal possible mechanisms that may result in thiazide-induced hyperglycaemia are elevated free fatty acid levels, which are known to decrease insulin secretion in response to glucose, significant reductions in insulin sensitivity and enhanced hepatic glucose production .and/or cate- cholamine secretion and action

The most practical approach for preventing thiazide- induced hyperglycaemia is to start with the lowest thiazide dosage and optimize serum potassium concentrations. Sometimes, thiazides should be used in combination with potassium supplements or potassium-sparing drugs, such asamiloride. If

ineffective, diuretics should be combined with another first-line .antihypertensive drug rather than being given at an increased dosage

♣Conclusion

Drug-induced hyperglycaemia is a growing concern, especially because of an increased use of older agents such as GCs or any another type of drug. It is uncertain whether this hyperglycaemia directly results from drug action or whether, in some (most?) instances, the medication simply unmasks pre-existing diabetes in individuals at high risk because of poor lifestyle habits. The exact mechanisms by which the implicated different between pharmacological classes, play a role in the development of diabetes.drugs cause hyperglycaemia and diabetes remain to be further investigated but appear to be multiple (targeting insulin secretion/sensitivity), and potentially complex. For some pharmacological classes, weight gain and/or AT dysfunction(adiposopathy) certainly Despite potential new-onset or worsening diabetes, the benefits of appropriately prescribed treatment with the five pharmacological classes of drugs discussed in the present review largely outweigh the potential risks of discontinuing therapy (as for statins). Nevertheless, clinicians should be mindful of the risk of deterioration of glucosehomeostasis, especially in individuals with pre-existing risk factors, so that alternative therapies with a lower risk of hyperglycaemia may be chosen whenever possible. Careful monitoring is recommended for high-risk individuals receiving agents known to impair glucose tolerance, with the goal of preventing diabetes or initiating early treatment and avoiding diabetes-associated complications. Lifestyle intensification remains a key step to prevent or treat drug-induced disturbances in glucose homeostasis; if insufficient, metformin remains the first-choice medication. Newer glucose-lowering agents that may promote weight loss are of potential interest in the treatment of individuals whose diabetes occurs in a context of weight gain and insulin resistance. For severe hyperglycaemia and of course DKA, a marker of profound beta cell dysfunction, insulin therapy becomes mandatory and should be adjusted according to close .blood glucose monitoring