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PHARMACOTHERAPY OF DPP4 INHIBITORS IN THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

Type 1 diabetes mellitus (DM) results from the pancreas' failure to produce enough insulin. Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. Diabetes is one of the most common diseases in the US. It is estimated that 16.7 million US adults (about 7% of the total adult US population) have diagnosed diabetes (Figure 1). Newly released statistics from the Centers for Disease Control and Prevention (CDC) illustrate that diabetes has risen by over 14 percent in the last two years. Acute symptoms of diabetes are due to severe hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss and blurred vision. The risk factors include: obesity, especially central (truncal) obesity, lack of physical activity. Type II diabetes causes peripheral insulin resistance means that although blood levels of insulin are high there is no hypoglycaemia or low blood sugar. This may be due to changes in the insulin receptors that bring about the actions of insulin. In TYPE-I Diabetes, there is beta cell deficiency leading to complete insulin deficiency. Thus it is termed as autoimmune disease where there are anti insulin or anti-islet cell antibodies present in blood. The complications include: kidney damage, heart problems, vision problems, and neurological problems.

INTRODUCTION:

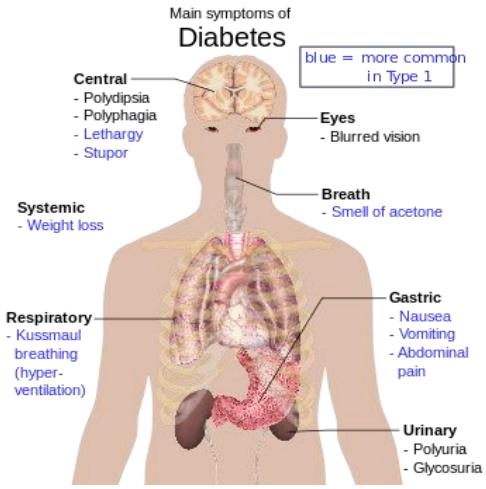
Diabetes is due to the reason the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. These includes three main types of diabetes mellitus which are as such: Type 1 DM results from the pancreas' failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes." The cause is unknown. Usually Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes." The primary cause is excessive body weight and not enough exercise.[1] Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels. Epidemiology speaks as diabetes is one of the most common diseases in the US. It is estimated that 16.7 million US adults (about 7% of the total adult US population) have diagnosed diabetes (Figure 1). (Newly released statistics from the Centers for

Disease Control and Prevention (CDC) illustrate that diabetes has risen by over 14 percent in the last two years. The CDC estimates that 20.8 million Americans -- 7 percent of the U.S. population -- have diabetes, up from 18.2 million in 2003. Nearly a third of these Americans are undiagnosed. If undiagnosed diabetes is included, it is estimated that more than 1 in 10 adults in the US has diabetes. Over 93% of patients with diabetes have type 2 (see Classification of Diabetes).

Diabetes Mellitus

These symptoms includes acute symptoms of diabetes are due to severe hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss and blurred vision. Patients may exhibit impaired growth and increased susceptibility to infections as well as chronic symptoms of diabetes are due to vascular damage from persistent hyperglycemia. Vascular damage leads to end-organ damage. Other conditions associated with diabetes, such as hypertension, dyslipidemia (as well as smoking) accelerate the development of vascular damage and the chronic complications of diabetes, which are the following:

Microvascular complications are a significant cause of morbidity. Persistent hyperglycemia is the major cause for the microvascular complications which are highly specific for diabetes. Retinopathy with potential loss of vision, nephropathy leading to kidney failure, peripheral neuropathy leading to pain, foot ulcers, and limb amputation, autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction.[2] Macrovascular complications are the main cause of mortality. Although persistent hyperglycemia may contribute to macrovascular complications, it is the associated conditions (hypertension, dyslipidemia, smoking) that account for most of the burden of the macrovascular complications. Coronary heart disease which is the major cause of death for patients with diabetes, peripheral vascular disease, cerebrovascular disease.

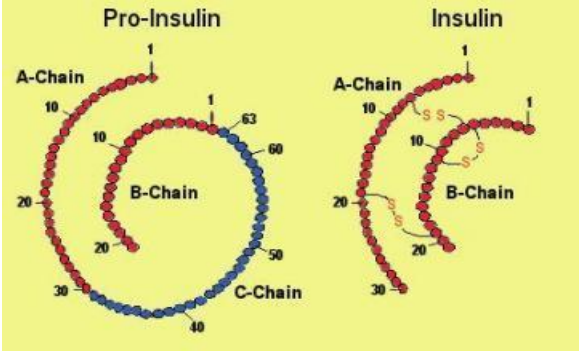


Diagnosis of Diabetes and Glucose Intolerance

Diabetes is a dysmetabolic disorder affecting multiple bodily functions. Its diagnosis is based on the presence of hyperglycemia. The diagnostic criteria for diabetes were modified in 1997 and again in 2003 by the American Diabetes Association, as shown in Table 1. The criterion for FPG was derived from the strong association of FPG with retinopathy in various populations with a high prevalence of diabetes (such as the Pima Indians in Arizona). The cutoff value of FPG ≥**126** mg/dl was chosen to separate the bimodal distribution of the rate of chronic complications.[3]

Physiology of Insulin Release and Action

The endocrine pancreas consists of the islets of Langerhans, which are small endocrine glands scattered throughout the



pancreas. The four different types of islets and its secretory products are shown in Table 2. We will review only insulin here.

Insulin Synthesis and Secretion

The beta cell synthesizes pro-insulin which is converted to insulin and C-peptide after proteolytic cleavage (figure 2). Both C-peptide and insulin are released in the circulation in equimolar amounts. This is the major site of regulation of circulating insulin. C-peptide has no known biological activity. A very small amount of pro-insulin is also secreted n the circulation. Insulin is a 51-amino acid peptide with 2 chains connected by a disulfide bond. Insulin's half-life is 3-5 minutes and about 50% of it is cleared in a single pass through the liver. [4] **Other actions of insulin include:** cell growth regulation, beta cell survival and development, food intake regulation, reproduction. Typical of other receptors, insulin receptors have an extracellular domain that binds insulin and a cytoplasmic domain that initiates the complex intracellular signal transduction pathway that gives rise to its various effects. Defects in the signal transduction pathway that cause diabetes have been described. [5] Clearance of insulin is achieved primarily via its receptors. About 50% of insulin is cleared in a single pass through the liver. Some clearance is via the kidney. [6]

Risk factors for type 2 diabetes

Obesity, especially central (truncal) obesity, Lack of physical activity., Ethnicity: people of South Asian, African, African-Caribbean, Polynesian, Middle-Eastern and American-Indian descent are at greater risk of type 2 diabetes, compared with Drug therapy - eg, combined use of a thiazide diuretic with a beta-blocker.

Low-fibre, high-glycaemic index diet., Metabolic syndrome., Polycystic ovary syndrome, Family history (2.4-fold increased risk for type 2 diabetes).

Adults who had low birth weight for gestational age. Statins have been associated with a small, but statistically significant risk of new-onset diabetes. Patients with risk factors for developing diabetes mellitus may be at higher risk. This risk is likely outweighed by the benefits of reducing cardiovascular risk.

Table 2. Endocrine cell types in pancreatic islets of Langerhans

Islet Cell Type	Secretory Products
A cell (alpha)	Glucagon
B cell (beta)	Insulin
D cell (delta)	Somatostatin
F cell	Pancreatic Polypeptide

Classification of Diabetes

Knowledge of the physiology of insulin release and action helps us think about the pathophysiology of diabetes. Similar to other endocrine conditions, any defect along the pathway will results in abnormal fuel metabolism, which will be manifested primarily as hyperglycemia. [7] In 1997, the American Diabetes Association revised the nomenclature for the major types of diabetes. These terms had been confusing and had frequently resulted in classifying the patient based on treatment rather than etiology. The new **classification of diabetes based on etiology** is shown below:

Type 1a diabetes: Pancreatic beta islet cell destruction leading to absolute insulin deficiency autoimmune (most common) idiopathic (rare)

Type 1b presents like type 1 (with DKA), then behaves like type 2

Type 2 diabetes: varying degrees of insulin resistance and insulin deficiency

Other specific types

Maturity onset diabetes of the young (MODY): Currently 6 monogenetic defects of beta cell function defined with defects in islet cell glucokinase or in various transcriptions factors such as HNF-1alpha, HNF-4alpha, IPF-1. The end result is impaired insulin release and hyperglycemia.

Autosomal dominant pattern. Onset of hyperglycemia generally before age 25.

Genetic defects in insulin action: Mutant insulin gene, insulin exhibits impaired receptor binding (rare) Mutation of insulin receptor. Often associated with acanthosis nigricans (thickening and discoloration of skin) and some forms of polycystic ovarian syndrome (uncommon).

Diseases of the exocrine pancreas: Need extensive damage to pancreas for diabetes to occur. Includes trauma, infection, chronic necrotizing pancreatitis and pancreatic carcinoma, cystic fibrosis and hemochromatosis. May be another mechanism besides simple beta cell reduction since cancers which involve a small part of the pancreas may lead to diabetes (paracrine inhibition of insulin release)

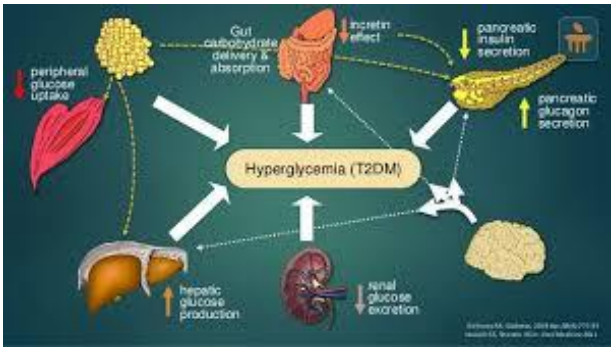
Endocrinopathies: Includes acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma. Caused by excess secretion of hormones which antagonize insulin including growth hormone, cortisol, glucagon and epinephrine.

Drug/chemical induced diabetes: Many drugs may impair insulin resistance or insulin secretion leading to diabetes in predisposed individuals. Major drugs include synthetic glucocorticoids, cyclosporin A, nicotinic acid, interferon, pentamidine, occasionally thiazide diuretics.

Infections: Congenital rubella is the most common virus implicated in the development of diabetes. Coxsackie virus B, adenovirus, mumps and cytomegalo virus have all been implicated in inducing certain cases of the disease.

General Pathophysiology

Diabetes occurs when there is an imbalance between the demand and production of the hormone insulin. When food is taken, it is broken down into smaller components. Sugars and carbohydrates are thus broken down into glucose for the body to utilize them as an energy source. The liver is also able to manufacture glucose. [8]



In normal persons the hormone insulin, which is made by the beta cells of the pancreas, regulates how much glucose is in the blood. When there is excess of glucose in blood, insulin stimulates cells to absorb enough glucose from the blood for the energy that they need. [9]

Insulin also stimulates the liver to absorb and store any excess glucose that is in the blood. Insulin release is triggered after a meal when there is a rise in blood glucose. When blood glucose levels fall, during exercise for example, insulin levels fall too. [10]

High insulin will promote glucose uptake, glycolysis (break down of glucose), and glycogenesis (formation of storage form of glucose called glycogen), as well as uptake and synthesis of amino acids, proteins, and fat. [11]

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

Pathophysiology of type 1 diabetes

In this condition the immune system attacks and destroys the insulin producing beta cells of the pancreas. There is beta cell deficiency leading to complete insulin deficiency. Thus it is termed an autoimmune disease where

there are anti insulin or anti-islet cell antibodies present in blood. These cause lymphocytic infiltration and destruction of the pancreas islets. The destruction may take time but the onset of the disease is rapid and may occur over a few days to weeks. [12]

There may be other autoimmune conditions associated with type 1 diabetes including vitiligo and hypothyroidism. Type 1 diabetes always requires insulin therapy, and will not respond to insulin-stimulating oral drugs. [13]

Pathophysiology of type 2 diabetes

This condition is caused by a relative deficiency of insulin and not an absolute deficiency. This means that the body is unable to produce adequate insulin to meet the needs. There is beta cell deficiency coupled with peripheral insulin resistance. Peripheral insulin resistance means that although blood levels of insulin are high there is no hypoglycaemia or low blood sugar. This may be due to changes in the insulin receptors that bring about the actions of the insulin. [14] Obesity is the main cause of insulin resistance. In most cases over time the patients need to take insulin when oral drugs fail to stimulate adequate insulin release.

ROLE OF DPP4 INHIBITORS AS THERAPEUTIC AGENTS

As a therapeutic class, the DPP-4 inhibitors comprise a diverse group of compounds, which can be broadly divided into those that mimic the dipeptide structure of DPP-4 substrates and those which are non-peptidomimetic. [16] Compounds such as sitagliptin (β-amino acid based), and vildagliptin and saxagliptin, which are nitrile-containing inhibitors, belong to the former class, whereas alogliptin (modified pyrimidinedione) and linagliptin (xanthine-based) are members of the latter. The compounds which have been developed for therapeutic use are all competitive reversible inhibitors, which display high affinity for DPP-4, resulting in inhibition constants (Ki) in the low nanomolar range. There are, however, differences in the way in which they interact with the enzyme. DPP-4 is a member of a family of proteases, two of which (DPP-8 and -9) have been implicated in preclinical toxicities and suppression of T-cell activation and proliferation in some [30,31], but not all [20] studies; in order to minimize any potential off-target side effects, the inhibitors intended to be used therapeutically have, therefore, been chosen with this in mind (Table 3). Thus, in this respect, sitagliptin and alogliptin can both be described as being highly selective; they essentially show no inhibitory activity against other members of the DPP-4 family when tested in vitro.[17] Vildagliptin and saxagliptin are somewhat less selective with regard to inhibition of DPP-8/9 in vitro, although whether this has any significance in vivo is questionable because DPP-8/9 are located intracellularly. Linagliptin, while being selective with regard to DPP-8/9, is less selective with regard to fibroblast activation protein-α (FAPα)/seprase. FAPα is an extracellular enzyme which is not generally present in normal adult tissue (although it is expressed in stromal fibroblasts and upregulated during tissue remodelling). However, the extent of any FAPα inhibition in vivo with the therapeutic dose of linagliptin in humans has not been reported.

In general, the DPP-4 inhibitors have not been reported to result in any meaningful activation or inhibition of the CYP enzyme system, suggesting that they are unlikely to be involved in clinically meaningful drug interactions involving these systems. There are data suggesting that there is no great propensity for the DPP-4 inhibitors to be involved in any clinically relevant drug–drug interactions with other commonly prescribed medications, including metformin, pioglitazone, rosiglitazone, glyburide and simvastatin, suggesting that these agents can be co-administered with the DPP-4 inhibitors without the need for dose adjustment of either drug. As mentioned, CYP3A4/5 is involved in the conversion of saxagliptin to the active metabolite (BMS-510849), and strong inhibitors of CYP3A4/5, such as ketoconazole, increase

the exposure to the parent compound. For this reason, dose reduction by half (2.5 mg qd) is recommended when saxagliptin is co-administered with strong CYP3A4/5 inhibitors. Linagliptin is also a substrate for CYP3A4, and ketoconazole prevents the generation of the metabolite, CD1790. However, because this is of only minor importance in the clearance of linagliptin, inhibition or induction of CYP3A4 by concomitantly administered drugs was not considered likely to alter the overall exposure to linagliptin. Additionally, linagliptin has been identified as a weak competitive and a poor-to-moderate mechanism-based inhibitor of CYP3A4, resulting in a decrease in the clearance of other compounds metabolized by this pathway by less than twofold; linagliptin was therefore considered to have only a weak potential for clinically relevant interactions with drugs metabolized by this system. [18]

SAFETY OF DPP4 INHIBITORS

Some differences between the different DPP-4 inhibitors have arisen from preclinical safety studies and observations made during the course of the clinical trial programmes. Thus, vildagliptin and saxagliptin, but not sitagliptin or alogliptin, were reported to be associated with adverse skin. At the time of initial registration of vildagliptin (in EU), a meta-analysis of the clinical trial data revealed that the 100 mg q.d. dose was associated with small numerical elevations in liver transaminases compared to placebo or 50 mg b.i.d. For this reason, the recommended therapeutic dose was changed to 50 mg b.i.d., with the recommendation that liver function tests be performed before initiation and at three monthly intervals for the first year of treatment and periodically thereafter. Subsequently, the trend for mild increases (greater than three times the upper limit of normal) in liver enzymes was confirmed in the larger pooled safety analysis, but notably, this was not associated with any increased incidence of actual hepatic adverse event. Nevertheless, liver function tests are still recommended and vildagliptin is not approved for use in patients with hepatic insufficiency. Despite the above observations, overall, the DPP-4 inhibitors as a class appear to be very well tolerated, and rates of adverse effects have been low, and generally not different to placebo or comparator. An early meta-analysis of incretin based therapies (in which inhibitor data were available only for sitagliptin and vildagliptin) did, however, suggest that there was an increased risk of some infections (urinary tract infections with both inhibitors and nasopharyngitis more evident with sitagliptin) and headache (more evident with vildagliptin). [19] As might be expected from their similar efficacy in inhibiting DPP-4 activity (see above), broadly speaking, the DPP-4 inhibitors all seem to show similar efficacy in lowering HbA1c levels, although it must be stressed that these are observations made in different studies and so must be interpreted with some caution (figure 3). At present, data are available only from one direct head-to-head comparison between the inhibitors, in which the efficacy of saxagliptin and sitagliptin as add on therapy in metformin-treated patients was compared. This showed non-inferiority of saxagliptin to sitagliptin in terms of HbA1c lowering (−0.5 vs. −0.6% from a baseline of ∼7.7%; i.e. from 60 to 55 mmol/mol for saxagliptin vs. from 61 to 54 mmol/mol for sitagliptin) at week 18 with similar proportions of subjects (26 vs. 29%) reaching target HbA1c levels of <6.5 %.[20]

CONCLUSION

The DPP-4 inhibitors are the first new therapeutic class of oral antihyperglycaemic drug for T2DM for many years. They were designed for the treatment of the disease based on prior knowledge of the physiology of the incretin hormone GLP-1 and an understanding of the target (DPP-4), contrasting with the development of other antidiabetic agents whose blood glucose-lowering effects were initially discovered more by chance than by design without fully knowing the underlying mechanisms (e.g. metformin, sulphonylureas and glitazones). Identification of the 3-dimensional/tertiary structure of the DPP-4

protein allowed the rational design of small molecule inhibitors which interact only with the catalytic site without interfering in any of the other functions of the DPP-4/CD26 molecule. This, together with the understanding of the role of GLP-1 in glucose homeostasis and its unique susceptibility to cleavage by DPP-4, probably accounts for the remarkable lack of adverse effects so far associated with the therapeutic use of the DPP-4 inhibitors. As a class, the DPP-4 inhibitors comprise of a group of chemically diverse compounds, which differ in terms of their potency to inhibit the DPP-4 enzyme, their duration of action and their metabolism and elimination, as well as isolated compound-specific characteristics. They are all apparently well tolerated (side-effect profile resembles placebo) and result in clinically meaningful reductions in blood glucose (fasting and postprandial) and HbA1c levels, with minimal risk of hypoglycaemia and without weight gain—in this latter respect, they are better than all other agents except metformin and the incretin mimetics. They are used without the need for dose titration and give broadly similar HbA1c lowering efficacy to other oral antidiabetic agents; they are compatible with first-line therapy and they give predictable additivity to other agents, where they can be used without dose adjustment of either agent. At present, although there are some practical differences between the different DPP-4 inhibitors with respect to dosing frequency and their ability to be used in different patient subpopulations, there seems to be little to distinguish between them in terms of their efficacy as antidiabetic agents and their safety. Only long-term accumulated clinical experience will reveal whether compound-related characteristics lead to any clinically relevant differences. Although diabetes is a slow killer with no known curable treatments, its complications can be reduced through proper awareness and timely treatment. It is important to keep the blood glucose levels of patients under strict control for avoiding the complications. One of the difficulties with tight control of glucose levels in the blood is that such attempts may lead to hypoglycemia that creates much severe complications than an increased level of blood glucose.

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