The Effect of Metformin on C-Reactive Protein In Patients with Type 2 Diabetes Mellitus

Thesis submitted for the partial fulfilment of
Master degree in Pharmaceutical Science (Clinical Pharmacy)

By the pharmacist

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Diabetes

Etiology

The word diabetes is taken from Greek diabaínein, and literally means "passing through", a reference to one of diabetes' major symptoms of excessive urine discharge. The word became "diabetes" from the English adoption of the Latin diabetes. In 1675 Thomas Willis added mellitus to the name (Greek mel, "honey" or "sweet") when he noted that a diabetic's urine and blood has a sweet taste. In 1776 Matthew Dobson confirmed the sweet taste because of an excess of sugar in the urine and blood of people with diabetes (Rother, 2007).

Definition

Diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the insulin hormone made in the beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action (Rother, 2007). High blood sugar levels over long periods of time can cause complications such as: damage to blood vessels, kidneys, and difficulties with circulation (Finch, 2003).

Prevalence of Diabetes:

In 2006, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes. Its incidence is increasing rapidly, and it is estimated that by the year 2030, this number will double. Diabetes mellitus

occurs throughout the world, but is more common (especially type 2) in the more developed countries (Marc Santora, 2006).

Diabetes is in the top 10, and perhaps the top 5, of the most significant diseases in the developed world. Around 4 million deaths every year are attributable to diabetes, most diabetics die from other chronic conditions, such as cardiovascular disease (Edmundson, 2006).

The top 10 countries, in numbers of sufferers, are India, China, USA, Indonesia, Russia, Japan, UAE, Pakistan, Brazil and Italy (White et al, 2000).

Etiologic classification of diabetes mellitus:

Type 1 diabetes

Type 1 diabetes was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that synthesize insulin hormone that regulates blood glucose level. Insulin hormone "unlocks" the cells of the body, allowing glucose to enter and fuel them. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. It is two types:

- Immune mediated
- Idiopathic

Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes (Narendran et al, 2005).

Type 2 diabetes

Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes. It usually begins as insulin resistance,

(a disorder in which the cells do not use insulin properly), combined with relative insulin deficiency. Therefore, an individual with type 2 diabetes may have a combination of deficient secretion and deficient action of insulin. (Allan, 2008).

Gestational diabetes

Gestational diabetes mellitus is defined as glucose intolerance or diabetes mellitus diagnosed for the first time during pregnancy.It results from the women inability to mount sufficient insulin secretion to compensate for the increased nutritional needs of gestation, the increased adiposity of pregnancy, and the anti-insulin hormones, specifically human placental lactogen, prolactin, cortisol and progesterone. In normal pregnancy, the insulin secretory response increases up to 4-fold to compensate for the diabetic forces of pregnancy(Griffin et al ,2002) Gestational diabetes affects about 4% of all pregnant women . After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes (Buekens, 2004).

Other specific types of diabetes:

Diabetes may be caused due to other disorders, diseases or etiological agents:

-Genetic defects of β-cell function (Francesca et al, 2007).

-Genetic defects in insulin action (Lann and LeRoith, 2007)**.**

-Diseases of the exocrine pancreas (Durie , 2003).

E.g.:Trauma/pancreatectomy,Pancreatitis,Hemochromatosis.

-Endocrinopathies (Koike et al, 2003).

E.g.: Acromegaly, Cushing's syndrome, Pheochomocytoma, Glucagonoma, Aldosteronoma, Hyperthyroidism.

-Drug or chemical-induced (Gentile et al, 2002).

E.g.: Nicotinic Acid, Glucocorticoids, Thiazide Diuretics, Beta-adrenergic agonists, Atypical antipsychotics, Diazoxide, Interferon alfa, Phenytoin.

-Infections (Viscari et al, 2003).

E.g.: Congenital rubella, Cytomegalovirus.

-Immune mediated diabetes (Diego et al, 2003).

E.g.: "Stiff-man" syndrome, Anti-insulin receptor antibodies.

-Other genetic syndromes sometimes associated with diabetes (Tobon et al 2006).
E.g.: Down syndrome, Klinefelter syndrome, Turner syndrome.

Diabetes Symptoms

Diabetes is sometimes discovered accidently in people who have no symptoms. About 40 percent of type 2 diabetics have no obvious symptoms of diabetes (Engelgau et al, 2000). Some people with diabetes have a variety of symptoms. These symptoms include: excessive thirst, frequent urination, dry skin, weight loss, frequent feeling of tiredness, slow healing of infections, blurred vision, and tingling in the hands or feet (Harris et al, 2003).

Diagnosis

Criteria for the diagnosis of diabetes (Griffin et al, 2000).

1- A1C $\geq$ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified. OR

2. FPG $\geq$126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. OR

3. Two hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Risk factors

Type 2 diabetes risk factors include :(Hussam et al, 2005).

- Age - Older than 40 years: Age appears to be the most important risk factor for the development of type 2 diabetes mellitus.
- Obesity - Weight greater than 120% of desirable body weight.
- Family history of type 2 diabetes in a first-degree relative.
- Hypertension (>140/90 mm Hg) or dyslipidemia (HDL<35 mg/dL (0.90 mmol / L) or triglyceride level >250 mg/dL) (2.83 mmol / L).
- Use of diabetogenic drugs, e.g. corticosteroids, oestrogens.

Complications:

Cardiovascular disease

Cardiovascular diseases are the major complications and the leading causes of premature death among diabetic people (about 75 percent of diabetic people die from heart diseases). Middle-aged adults with type 2 diabetes are two to four times more likely to die from heart disease than non-diabetic adults (Gaede et al, 2003).

Kidney disease

Diabetes is a leading cause of renal nephrophathy, which can lead to end-stage renal disease (ESRD). This is a serious condition which may result in the need for dialysis or kidney transplantation (Van , 2009).

Blindness

Diabetes is a major cause of blindness.Diabetic retinopathy alone accounts for at least 12 percent of new cases of blindness each year. People with diabetes are 25 times more at risk for blindness than the general population (Fong et al, 2004).

Nervous system disease

Around 60 to 70 percent of diabetics have some type of nervous system damage or neuropathy, which includes decreased sensation in feet or hands or carpal tunnel syndrome (Pliquett et al, 2004).

Infections

Poorly controlled diabetics are prone to infections, especially in the skin with mucocutaneous candidiasis (Martin et al, 2004).

Dyslipidemia

Lipid profile should be conducted at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. (Arshag, 2009).

Hypertension

BP should be measured at every diabetes visit (Adler et al, 2000).

Hypoglycaemia

It occurs when blood glucose levels fall to less than 3.0 mmol/L. It occurs in type 2 diabetics due to oral hypoglycaemic drugs, notably sulfonylureas (Cryer, 2004).

Sever hyperglycemia

Extremely high blood sugar levels can lead to a dangerous complication called hyperosmolar syndrome, also known as hyperosmolar hyperglycemic state (HHS), or hyperosmolar coma. Hyperosmolar syndrome is a life-threatening form of dehydration that can result from untreated high blood sugar levels (Quinn, 2001).

Treatment

The ADA- EASD guidelines declared that Lifestyle interventions have multiple beneficial effects and do not cost much, but are usually insufficient alone. Metformin is recommended as it is economical, weight stable, and does not cause hypoglycemia. It cause gastrointestinal side effects, reduce vitamin B_{12} absorption, metformin associated lactic acidosis, and is contraindicated in renal dysfunction (Nathan et al, 2008).

Therapy divided into two tiers: tier 1, which has well-validated, effective and cost effective treatments, and tier 2, which lists less well validated drugs.

TIER 1(Karla et al, 2009)

Tier 1, step 1 is lifestyle intervention and metformin, with detailed advice on titration of metformin (begin from 500mg or 850mg per day, and increase every 5-7 days, as required, to a maximum of 2.5 g/day over 1-2 months)

If step 1 fails to achieve or sustain glycemic goals, one should add insulin or sulfonylurea (step 2), within 2-3 months of therapy initiation, or at any time when target is not achieved, or if metformin is contraindicated or not tolerated.Insulin is preferred in patients with HbA1c > 8.5%, or in those with symptoms secondary to hyperglycemia.

Step 3 is to start, or intensify insulin therapy, as the case may be, using short or rapid-acting insulin, while stopping or tapering off secretagogues. The guidelines clearly discourage triple oral hypoglycemic combinations.

TIER 2 (Karla et al, 2009)

Step 1 is to focus on the advantages of proglitazone and exenatide in avoiding hypoglycemia, and the weight loss associated with exenatide.

In tier 2, step 2 is to add metformin and pioglitazone, or metformin and GLP-1 agonist to lifestyle measures. Step3 will be to give a triple drug oral combinations (metformin+pioglitazone + sulfonylurea) or metformin + basal insulin in addition to lifestyle therapy.

Medication

If control of the blood glucose level has not been possible with lifestyle changes then some drugs may be necessary.

1-Alpha-glucosidase inhibitor -eg: Acarbose(Lucassen and Akermans, 2005).

2- Biguanide -eg: Metformin (Vigneri and Goldfine, 2000).

3- Insulin secretagogues (Monami et al, 2007).

A-sulfonylureas -eg: gliclazide, glimepiride, glyburide.

B-nonsulfonylureas -eg: nateglinide, repaglinide.

4- Insulin sensitizers -eg: pioglitazone, rosiglitazone (David , 2001).

5-Insulin may be used as initial therapy in type 2 diabetes, especially in cases of marked hyperglycemia (A1C >9.0%) (Bell, 2004).

6- Incretin based therapy -eg: exendin-4, liraglutide, vildagliptin, sitagliptin (Laurence et al, 2009).

Diabetes & Inflammation

Type 2 Diabetes as an Inflammatory Disease

The origin of type 2 diabetes is complex. To date, two main causes had been identified: modifications to insulin secretion in response to glucose, and organ insensitivity to the insulin produced by the pancreas (Leonard et al, 2005).

New research shows inflammation plays an essential role in the development of type 2 diabetes; they have now found a link between inflammation and diabetes (Francesco et al, 2004).

Indeed, several cross-sectional studies have shown an increased prevalence of inflammatory markers in persons with diabetes. More recently, it has been shown that inflammatory markers measured at baseline (in nondiabetic subjects) predict the development of diabetes several years later. The increased risk of the development of diabetes in the presence of markers of inflammation can be two to six folds (Aggarwal et al, 2003).

New theories that link between Type 2 Diabetes and Inflammation

First:

A new gene called islet-brain 1 (IB-1) has been identified. It was observed that insulin producing cells do not behave normally in the presence of a mutated IB-1 gene. The cell becomes more vulnerable to stress and dies more easily than a non-mutated cell (Trayhurn and Beattie, 2001).

This IB-1 mutation is also responsible for a decrease in insulin synthesis and may provoke diabetes in two ways. First, by contributing to insulin production disorders which occur very early in type 2 diabetes. Second, the mutation may play a role in the gradual destruction of insulin-secreting cells. Although IB-1 mutations are rare, expression of this gene does seem to be blocked by the chronic hyperglycemia of diabetics and it could, therefore, play a major role in type 2 diabetes (Gérard and Philippe, 2000).

Second:

A novel protein, named Tanis, is implicated in type 2 diabetes and inflammation. Tanis is expressed in the liver in inverse proportion to circulating glucose and insulin levels and in direct proportion with plasma triglyceride concentrations (Gao et al, 2003). Hepatic Tanis gene expression was markedly increased (3.1fold) after a 24-h fasting in diabetic but not in nondiabetic persons .In addition, glucose inhibited Tanis gene expression in cultured hepatocytes as well as in several other cell types. Thus, Tanis seems to be regulated by glucose and is dysregulated in the diabetic state (KenWalder et al, 2002).

Third :

Eating induces an inflammatory state in everyone. Normally, inflammation occurs for three or four hours after eating but will then taper off. Hu stated that, "If people eat every three or four hours, they spend most of their time in a pro-inflammatory state which may lead to type 2 diabetes if it is continued for a long time" (Hu et al, 2001).

Forth:

Chronic inflammations result from link between diabetes and obesity.Fat cells don't just store fat; they secrete various components into the blood stream, including cytokines and inflammatory markers, which serve to stimulate further release of inflammatory markers which cause inflammation. Researchers think that cytokines interfere with insulin receptors, which would account for insulin resistance and point to the inflammatory process as an important underlying cause of type 2 diabetes (Greenberg , 2006).

Obesity, Inflammation and Diabetes

Obesity has also become a public health priority, given its growing worldwide epidemic and its vast health consequences. Thus, the pathogenesis of so-called "diabesity"has recently received increased attention (Kaye and Francine, 2005).

Excess adiposity is the most important risk factor for the development of insulin resistance and type 2 diabetes. It has been proposed that inflammatory cytokines secreted by adipose tissue exert an endocrine effect conferring insulin resistance in liver, skeletal muscle, and vascular endothelial tissue, ultimately leading to the clinical expression of type 2 diabetes (Xu, 2003).

It was indicated that 80–90 percent of people with type 2 diabetes are obese, and a sustained 15-pound weight loss is associated with a 60 percent reduction in risk (Esposito et al, 2003).

It has been proposed that obesity is linked to diabetes through the following mechanisms:

1- Adipocytes, especially in the obese, secrete a number of cytokines recently dubbed "adipokines" such as tumor necrosis factor (TNF) and interleukin (IL)-6, leads to an acute-phase response with increased hepatic production of C-reactive protein (CRP), a sensitive marker of low-grade systemic inflammation.Women with the highest levels of TNF-alpha receptor 2 had a 64 percent increased risk of diabetes, and women with the highest levels of interleukin-6 had a 91 percent increased risk compared to women with the lowest levels (Waleed and Osama, 2003).

2-Some adipocytokines may also cause vasoconstriction. Vasoconstriction appears to diminish insulin action. In fact, arteriolar constriction, seen in the retina, has recently been shown to predict diabetes (Gualillo et al, 2006).

3-Obesity also decreases adipocyte expression of adiponectin, which has anti-inflammatory and insulin-sensitizing effects (Krakoff et al, 2003).

4- Researchers demonstrate "Fat cells don't just store fat; they secrete various components into the blood stream, including cytokines, which cause inflammation," Cytokines are incriminated to interfere with insulin receptors, which would account for insulin resistance and point to the inflammatory process as an important underlying cause of type 2 diabetes" (Marette, 2002).

Low-Grade Systemic Inflammation and the development of Type 2 Diabetes

It was indicated that subclinical elevations of CRP, IL-6, orosomucoid, and sialic acid are related to the development of diabetes. An inflammation score composed of these four markers plus white cell count and fibrinogen showed the association of inflammation with diabetes (Bruce Duncan et al, 2003).