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EDITORIAL

Metformin; Recent Interest in an Old Drug.

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In the last decade, the management of type 2 diabetes has usually been successful by the use of many oral drugs from different drug classes. The success of these drugs does not depend only on their hypoglycemic effect, but also on their immediate side effects and long use sequels.

This concept was true for the biguanide metformin which was used for about 40 years. However, the Food and Drug Administration (FDA) approval was restricted because of the risk of lactic acidosis associated with the use of an earlier biguanide, phenformin (1). Later on, the UK Prospective Diabetes Study Group published in 1998, that lactic acidosis is extremely rare with metformin (2-5).

In the same year, thiazolidinedione drugs as rosiglitazone (Avandia), were introduced in the market to lower blood glucose levels and glycated hemoglobin levels (6).

However, recent reports of adverse effects on the cardiovascular system were published with a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo (7). Thiazolidinediones causes volume overload and are known to precipitate congestive heart failure in susceptible patients and also produces a modest reduction in the hemoglobin level (8). More recently Nissen (9), in a meta-analysis including 42 trials, concluded that rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

The recent interest in metformin rose after it was proved to have a very low incidence of lactic acidosis, beneficial effects on microvascular and macrovascular complications of diabetes, improving endothelial function and reduced proinflammatory responses in atherosclerotic heart disease, heart failure and also in the metabolic syndrome.

Many studies on metformin showed its beneficial effects in polycystic ovary syndrome, weight loss and leptin sensitivity, incidence of tumors, reducing thyrotropin in hyperthyroidism and safety of use with psychiatric illness.

Lactic Acidosis

It is characterized by an elevated blood lactate concentration (>45.0 mg/dL [>5.0 mmol/L]), decreased blood pH (<7.35), and electrolyte disturbances with an increased anion gap.

Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate, and the accumulation of lactic acid may intensify under certain circumstances. Diabetes itself predisposes to lactic acidosis (10,11).

Metformin, however, differs from phenformin in molecular structure and pharmacokinetics and, unlike phenformin, is thought to enhance glucose oxidation without substantially affecting fasting lactate production in peripheral tissues.

Cardiovascular effects

Micro and Macrovascular Complications:

Type 2 diabetes is usually accompanied with obesity, hypertension, glucose intolerance, insulin resistance, and dyslipidemia with elevated triglycerides (TG), low levels of high density lipoprotein [HDL], and elevated low-density lipoprotein [LDL] (12).

Hyperglycemia through a series of chemical reactions, ultimately generates higher molecular weight condensates known as advanced glycation end products (AGE) that engage a cell surface receptor (RAGE). The engagement of RAGE can increase oxidative stress, bind cytokines and activate inflammatory functions of endothelial cells, smooth muscle cells, and macrophages, and cell types intimately involved in atherogenesis (13,14).

Treatments that lower blood sugar reduce the level of AGE and protect against diabetic microvascular complications such as nephropathy, retinopathy and neuropathy.

This is true with improvement of microvascular complications with any drug including insulin that controls blood sugar levels but will not reduce macrovascular manifestations (15).

However, many clinical trials, such as the University Group Diabetes Program (UGDP) and the United Kingdom Prospective Diabetes Study (UKPDS), among others, have found only limited, if any, relationship between glycemic control and diabetic macrovascular manifestations such as myocardial infarction. It was noticed in UKPDS that in patient on metformin monotherapy, the incidence of myocardial infarction decreased by 39% (16-19).

Studies on cultured human vascular smooth muscle cells and endothelial cells showed that metformin inhibit the

Abbreviations and Acronyms

AGE	= advanced glycation end products
CRP	= C-reactive protein
FDA	= Food and Drug Administration
IGT	= impaired glucose tolerance
PCOS	= Polycystic ovary syndrome

pro-inflammatory cytokines IL-6 and IL-8 responses and adhesion molecule genes by inhibiting NF- κ B activation via AMP-activated protein kinase (20).

Elevated glucose concentration also leads to an oxidative stress that favors mitochondrial permeability transition pore (PTP) opening and subsequent cell death. Daille, et al, 2005, proposed that metformin improves diabetes-associated vascular disease both by lowering blood glucose and by its effect on PTP regulation (21).

Obesity has been shown to be associated with increased oxidative stress and inflammatory mediators.

Plasma migration inhibitor factor (MIF) concentration and mononuclear cell (MNC) mRNA are consistent with proinflammatory and are elevated with obesity. Their concentrations are significantly related to BMI. The use of metformin suppressed the plasma MIF concentrations in the obese, suggestive of an anti-inflammatory effect of this drug (22).

It was reported that persons with impaired glucose tolerance have increased levels of C-reactive protein (CRP) and fibrinogen (20,23).

The reverse is true where increased levels of CRP and fibrinogen (24) have been shown to predict the development of type 2 diabetes in prospective studies.

The Diabetes Prevention Program (DPP) (25) examined a large population of participants with IGT who were randomly assigned to treatment with intensive lifestyle modification or metformin or placebo therapy. Intensive lifestyle reduced the incidence of type 2 diabetes by 58% and metformin reduced the incidence of type 2 diabetes by 31%.

The subclinical inflammation (C-reactive protein, CRP) marker and impaired coagulation have been associated with increased obesity and insulin resistance. In 3,234 adults with impaired glucose tolerance. The DPP group showed that the median changes in CRP from baseline to 1 year were -29 to -33% in the lifestyle group, -7 to -14% in the metformin group, and +5% in the placebo group (26). This indicates the important changes occurring because of a strict lifestyle in the development of type 2 diabetes and cardiovascular complication. However, it also stressed on the beneficial effects of metformin in these conditions.

Mather et al. (27) proved that metformin treatment improves endothelial function by improving insulin resistance. This supports the concept of the central role of insulin resistance

in the pathogenesis of endothelial dysfunction in type 2 diabetes mellitus.

Heart Failure

In newly treated diabetic patients over the age of 30 years, the reported prevalence of heart failure is 22% in a nationally representative sample of Medicare claims in the U.S (28).

In the past few years, patients who were taking metformin would be considered to be victims of "inappropriate" or "unsafe" prescribing. Metformin was considered "absolutely" contraindicated in such patients and thiazolidinediones are "relatively" contraindicated (29).

However, in a large databases on subjects using oral antidiabetic agents comparing metformin with sulfonylurea therapy, fewer deaths occurred in subjects receiving metformin (33%) versus sulfonylurea (52%) (30-32).

Polycystic Ovary Syndrome

(PCOS) is characterised by anovulation, infertility, and hyperandrogenism, irregular menstrual cycles, hirsutism, and acne. The condition occurs in about 5-10% of women of reproductive age, and is easily detected by ultrasound (33). About 40% of women with PCOS will have type 2 diabetes or impaired glucose tolerance (34).

Premature balding has been suggested to be the male equivalent of polycystic ovaries (35).

Studies on hyperinsulinemia suggested that it is a common pathogenetic factor for both PCOS and the metabolic syndrome (36).

Women with PCOS have an 11-fold increase in the prevalence of metabolic syndrome compared with age-matched controls (37).

On the other hand, it was also reported that fathers of all girls with PCOS had metabolic syndrome (38).

Meta-analysis reports showed that metformin used to treat type 2 diabetes was also effective in achieving ovulation and was advised as a first line agent in women PCOS (39).

Obesity

Weight gain is associated with a high risk of developing cardiovascular and metabolic diseases such as coronary heart disease, hypertension, diabetes, and dyslipidemia.

The adipose tissue is not only a body energy store but the adipocytes can produce many hormones including leptin, adiponectin, resistin, atrial natriuretic peptide, and angiotensinogen (40).

The hormone leptin acts in the central nervous system to promote weight loss by decreasing food intake and increasing

metabolic rate (41). It also increases the sympathetic nervous activity which may explain the relation of obesity and hypertension (42). However, obesity is accompanied by elevated serum leptin which is referred to as leptin resistance (43).

Metformin is well known to have an anorexic effect (44), reduces body weight (45) and decreases leptin concentration in morbidly obese subjects (46). Kim et al. (47) proved that metformin enhances leptin sensitivity and corrects leptin resistance in high-fat-fed obese rats and that a combination therapy including metformin and leptin would be helpful in the treatment of obesity.

From this review we can consider the role played by metformin in patients with type 2 diabetes as the protective aspect of aspirin in cardiovascular diseases. It has minimal metabolic adverse side effects and reduces micro and macrovascular complications. This is not related only to its glycemic control but also to the direct effect on cellular mitochondria, vascular endothelium and smooth muscle with reduction of cardiac proinflammatory markers. Our impression is that future researches will more highlight the mechanism and beneficial effects of metformin on adipocytes-leptin and other hormones and its true place in the management of metabolic syndrome and obesity.

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