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The hepatic insulin resistance.2 mechanisms are reduction of peripheral and produce and release insulin, the second and third mechanism is stimulation of pancreatic ß cells to levels in three ways, the first and most important these drugs are thought to lower blood glucose 1-2 % which is really comparable to insulin, 70% and their ability to lower A1c is between diabetes with a good response rate not less than most widely used oral hypoglycemic agents. The most common clinically significant side effect of sulphonylurea therapy is hypoglycemia, which may occur with increased exercise, delayed meals, or both. These episodes are generally mild and easily treated with food. 1

Back to the concern of the potential cardiac toxicity, we may notice that from the start of addressing this concern till now, we do not find any solid recommendations or guidelines strongly support this concern, on the contrary almost all guidelines still highly recommend the use of sulphonylureas in type 2 diabetes either alone or in combinations, I do not find any contradiction between the increasing needs to the use of insulin and the use of sulphonylureas, the most important issue is to achieve the target for blood glucose control.

More understanding of molecular biology helped the industry to improve the sulphonylurea drugs achieving more selectivity in blocking of KATP channels in ß cells. This selectivity was evident in one of the important papers published in 2001 indicating that a sulphonylurea drug like Gliclazide did not alter the cardiac (Kir 6.2/SUR2A) and vascular (Kir 6.2/SUR2B) channels.2

A recently published paper just one month ago in Diabetes Care did indicate the importance of the adherence to the oral therapy as patients with type 2 diabetes who do not obtain at least 80% of their oral antihyperglycemic medications across 1 year are at a higher risk of hospitalization in the following year.3

So in conclusion, what really matters is to TREAT TO TARGET, I mean A1c below 7%, and yes there is an increasing need for the use of insulin in type 2 diabetes but, sulphonylureas especially the recent ones are very important, reasonable price and relatively safe agents.

1 Heart 80:108-109 ( August ) 1998
3 Reimann F. Ashcroft FM, Gribble FM. Diabetes 50:2253-2259, 2001

Mahmoud Ashraf Ibrahim, MD
Editor, Middle East Edition
Diabetes mellitus is one of the most common chronic diseases in Egypt, as it affects about 7% of the general population. The liver is affected by diabetes largely as a consequence of altered metabolic processes and by drug hepatotoxicity, conversely, hepatic cirrhosis in particular, is associated with disorders of glucose metabolism. The problems of management of metabolic alterations in cirrhosis are due to the heterogeneity of patients with regard to the clinical stage (i.e. Child A, B or C), the etiology of liver disease (i.e. bilharzial, postnecrotic, or both, alcoholic, metabolic, etc.) and the nutritional state.

Liver disease caused by diabetic medications.

I- Insulin Secretagogues
A- Sulfonylureas:
Hepatotoxic effects of oral sulfonylurea agents are rare. The drug most frequently associated with hepatotoxicity is chlorpropamide, with reported hepatotoxicity incidence of 0.5 to 1.5%. The type of liver injury is a cholestatic hepatitis, which is also seen with other sulfonylurea agents such as tolazamide, tolbutamide, and glyburide. Chlorpropamide has also been reported to cause a granulomatous hepatitis, whereas acute viral-like hepatitis has been associated with glyburide.

The mechanism of oral sulfonylurea-induced cholestatic hepatotoxicity is believed to be an allergic hypersensitivity reaction. The sulfa moiety present in all of these agents is the antigen likely responsible for adverse reactions. Oral sulfonylurea agents associated with hepatotoxicity include the following: chlorpropamide, glyburide, tolazamide & glibenclamide. Sulfonylurea hepatotoxicity typically occurs within 1 to 5 weeks after the drug is started, and is manifested by fever, rash, jaundice, malaise, and hepatomegaly. Biochemical tests typically show an elevated bilirubin, a rise in alkaline phosphatase, AST, and ALT, with occasionally peripheral eosinophilia.

On histologic examination, portal tract displays a mixed inflammatory infiltrate including eosinophils. Centrilobular cholestasis, lobular inflammation, and occasional bile duct proliferation. Fibrosis is rare. On discontinuation of the offendins drug, patients generally improve over the next few months. Gliclazide modified release represents a new development in the second generation of sulfonylurea drugs is characterized by dual route of excretion being 60 - 70% by the kidney and 10-20% by the bile. It has minimal incidence of hypoglycemia and less incidence of weight gain.

B- Non sulfonylureas:
Both repaglinide and nateglinide stimulate insulin release from pancreatic β-cells through inhibition of K-ATP channel.

Repaglinide
- Repaglinide is a carbamoyl methyl benzoic acid (CMB A) derivative.
- Repaglinide is rapidly absorbed and eliminated after oral administration the maximum plasma level is reached within 30-60 minutes and the drug via the systemic circulation after approximately 3-4 hours.
  - Repaglinide is metabolized by the cytochrome p 450 3 A 4 isoenzyme system and is eliminated primarily via the bile. The elimination half-life (t 1/2) is approximately 1 hour.

Nateglinide
- Nateglinide (N-[trans-4-isopropyl-cyclohexyl-carbonyl]-Di-phenylalanine)
- Nateglinide is absorbed rapidly after oral administration, reaches peak plasma concentration in 1 to 2 hours, and has terminal half-life (t 1/2) of < 1.75 hours. It appears to undergo limited first-pass hepatic metabolism with approximately 75% absolute systemic bioavailability. It shows a high degree of plasma protein binding, and more than 80% of an oral dose is metabolised and excreted in urine. Somesh et al 2000 demonstrated in a single dose pharmacokinetics of nateglinide in subjects with liver cirrhosis that there is no statistically significant or clinically relevant alteration in pharmacokinetic parameters of nateglinide resulted from hepatic dysfunction and it was well tolerated, therefore adjustment of nateglinide dosage is not required in subjects with mild to moderate cirrhosis.
  - The lack of effect of hepatic dysfunction on the hepatic metabolism of Nateglinide is most probably due to:
    - The drug is highly bound (> 96%) to plasma protein.
    - The hepatic disease did not alter the free concentration of the drug.
    - The amount of free drug available for
metabolism was below the level that would saturate the metabolising enzymes, even if their activity was diminished to some extent by hepatic disease.13

II- Biguanides
• Biguanides have been claimed to exert their antihyperglycemic action through three classical mechanisms of action: 1- Reduction of glucose absorption from the gut.14 2- Suppression of gluconeogenesis.15 3- A supposed anorectic effect.16
• The suppression of plasma FFA levels and their oxidation at the level of the liver and the muscle is likely to relieve the inhibition of pyruvate dehydrogenase favouring glucose oxidation, this finding explains the marginal increment in blood lactate concentration that follows metformin treatment and therefore reduced incidence of lactic acidosis.16
As such mechanism of action of metformin is very different from that of phenformin, and drug causing inhibition of oxidative phosphorylation and shift to non oxidative glycolysis.16
• At the level of the liver, the reduction of the rate of FFA oxidation lowers the allosteric activation of several gluconeogenic enzymes and provide less energy for driving the de novo synthesis of glucose.17
• Metformin is taken two or three times daily and is associated with GI side effects, especially diarrhea, metallic taste and impaired vitamin B12 and folate acid absorption.18
• Metformin has not been associated with significant hypoglycemia or weight gain when used as monotherapy.17
Metformin therapy in over weight patients in the UKPDS also decreased the incidence of diabetes-related death and myocardial infarction.19 This beneficial effect may be related to effects of metformin independent of the anti hyperglycemic action. Metformin decreases platelet aggregation and improves plasma lipid profile.20 Lactic acidosis is the most serious adverse effect of biguanide therapy mainly phenformin, but it can also occur with metformin. Metformin causes a small increase in blood lactate concentration after meals (possibly arising from the intestine) and a small but significant increase in other gluconeogenesis precursors (pyruvate and alanine).
Metformin may accumulate in patients with renal impairment as its clearance mainly through the kidney, leading to pathological lactic acidosis. Metformin associated lactic acidosis is still sporadically reported and mortality rate is as high as 50%.17
The risk of this potentially fatal complication can be minimised by strict adherence to prescribing precautions and contraindications. For instance, metformin should not be used in patients in whom accumulation of the drug is likely (e.g. renal dysfunction) or those with hepatic dysfunction or conditions that predispose to development of hypoxia.14

III- Thiazolidinediones (Glitazones)
• Thiazolidinediones are a new class of agents that have been developed to treat type 2 diabetes. These drugs act as peroxisome proliferator - activated receptor gamma (PPARγ) agonist.
• Glitazones appears to mediate the insulin sensitizing effects by binding to and activating PPARγ, thus enhancing the production of a number of proteins that are important in the cell’s biological response to insulin.18 These include proteins involved in glucose transport and utilization as well as lipid metabolism.

Hepatotoxicity
Idiosyncratic hepatotoxicity with troglitazone came to attention of the regulatory agencies in the fall of 1997, seven months after marketing began in the United States. Seventy-four cases of jaundice and hyperbilirubinemia were reported to the Food and Drug Administration (FDA) in 1997. Additional cases of Jaundice, liver failure, and / or death in 1998 and 1999, despite several additional warning letters and move - stringent requirements to monitor liver function at very frequent intervals.19 The FDA concluded that 90 cases of liver failure were possibly or probably related to troglitazone therapy during the 3 years that it had been on the market. As a result of this analysis and the availability of rosiglitazone and pioglitazone. Both of which appear not to have liver toxicity. The FDA encouraged Parke-Davis company to withdraw troglitazone from the market, which it did on March 22, 2000.19
Troglitazone combine the glitazone structure with vitamin E-related moiety. This molecule generates a family of quinone metabolites that are unique among thiazolidinediones, troglitazone is concentrated 15-20 fold in the liver compared to plasma levels.20 Troglitazone and its metabolites are secreted into bile and undergo considerable biliary recirculation. The plasma half life is 16-34 hours, less than 3% is excreted in the urine.20 The clinical course of the troglitazone hepatotoxicity is unclear. Initial reports suggested that the hepatic reaction occurred within the first few months of therapy and was unlikely to occur in individuals on therapy longer than 1 year.20 The FDA data show that new-onset hepatic abnormalities can occur in individuals who were on troglitazone in excess of 1 year. The hepatotoxicity due to troglitazone progresses for a period of time, even after the drug has been discontinued. In most instances, the liver recovers after several weeks to months but, in some individuals, there has been a steady progression to liver failure. Examination of the clinical trial data presented to the FDA by the rosiglitazone and pioglitazone sponsors was remarkably devoid of any suggestion of hepatic toxicity. Figure (1) shows that the incidence of serum ALT elevations greater than three times the upper limit of normal in both rosiglitazone - and pioglitazone-treated patients was the same as in their appropriate placebo-or comparator-treated controls. To the present time, more than one million patients have been treated with rosiglitazone and there were no cases of hepatotoxicity in which rosiglitazone has been proven to be the cause.21
A similar situation occurs for pioglitazone. The available data indicates that hepatotoxicity is unique to troglitazone and is not a class effect of either thiazolidinediones or PPARγ agonists.\textsuperscript{21}

Rosiglitazone

Unbound oral clearance of Rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child - Pugh class B/C) compared with healthy subjects. As a result unbound c max and AUC 0-inf were increased 2-and 3 fold, respectively. The elimination half life for rosiglitazone was about 2 hour, larger in patients with liver disease compared with healthy subjects. Therapy with rosiglitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminases level (ALT > 2.5 x the upper limit of normal) at baseline.\textsuperscript{28} In controlled trials 0.2% of patients treated with troglitazone has elevation in ALT > 3 x the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators (sulfonylureas or metformin).\textsuperscript{27,28} This contrast with pre-approval clinical trials of troglitazone involving 2,510 patients –in which 1.9% patients taking troglitazone experienced ALT > 3x the upper limit of normal compared with only 0.6% taking placebo.\textsuperscript{29}

Pioglitazone:

Pioglitazone is well absorbed and is metabolised by the hepatic cytochrome p 450 enzyme system. The half-life of the drug is approximately 9 hours, but two active metabolites (M-III and M-IV) contribute to extended glucose lowering effects.\textsuperscript{29} Dosage adjustment is not necessary in patients with renal failure, or in those undergoing haemodialysis. In hepatic insufficiency, volume of distribution was increased, and c max was reduced. The main side effect of the drug is mild oedema that occurred in minority of patients. Weight gain was due to redistribution of fat from visceral bed to subcutaneous areas. The hepatotoxicity seen with troglitazone was not apparent in clinical trials with pioglitazone.\textsuperscript{30}

IV- Alpha-Glucosidase Inhibitors (AGIs):

Alpha-glucosidase inhibitors block the metabolism of digested polysaccharides, and lower the amount of carbohydrates absorbed in a meal. They inhibit enzymes involved in the conversion of disaccharides, polysaccharides and complex sugars into monosaccharides in the brush border of the small intestine.\textsuperscript{31} Acarbose, miglitol, or voglibose tablets must be administered with the first bite of food to be effective.\textsuperscript{32} They are not associated with either weight gain or hypoglycemia when used as monotherapy.\textsuperscript{33} AGIs frequently associated with gastrointestinal side effects, especially flatulence and diarrhea, which can adversely affect treatment adherence. Acarbose is practically unabsorbed (maximum 1-2%), no toxic systemic effect are to be expected.\textsuperscript{34} The notable rise in liver enzymes has been observed in clinical studies with acarbose at 3 x 100 mg/day. In other non-clinical studies, rare cases of reversible increase in transaminase have been reported (6/100,000) in Japan and USA, but on higher doses. Liver damage due to acarbose has never occurred, not even in diabetic with hepatic cirrhosis or chronic hepatitis.\textsuperscript{35}

Management of Diabetes with Chronic Liver Disease

1. Dietary Advice:

A well balanced diet consisting of 50-55% carbohydrates, 30% fats and 15-20% proteins. It is preferable to use complex carbohydrates. Low carbohydrate diets may aggravate insulin resistance and leads to impairment of insulin secretion. High caloric diet is advocated, as many patients with chronic liver disease are malnourished and especially during hospitalization or during intercurrent illness.

2. Oral Diabetic Medication

- It is important to avoid hypoglycaemia in such patients because of low glycogen stores in the liver and administration of glucagon may not effectively stimulate hepatic glucogenolysis in cirrhotic patients.
- Sulfonylurea drugs should be used with caution because they are metabolized by the liver. These drugs can cause severe hypoglycaemia because of accumulation of active metabolites that prolong plasma half-life & biological action. This is in particular with glibenclamide and chlorpropamide, which have long half-life.
- Gliclazide modified release is preferred due to low risk of accumulation and hypoglycemia. It is also excreted mainly by the kidney.
- Glipizide or nateglinide have shorter half-life, and excreted mainly by the kidney.
- Biguanides (metformin) should be avoided because they cause lactic acidosis in patients with liver disease.
- Acarbose (AGI) could be prescribed as it doesn’t cause hypoglycaemia, lactic acidosis or rise in liver enzymes.
- The newer thiazolidinediones, rosiglitazone and pioglitazone were approved for treatment of type 2 diabetes in 1999. Pre-manufacturers recommend that the liver function tests should be checked every 2 months during the first year of use and periodically thereafter. If Jaundice develops or ALT increases to three times the upper limit of normal then the drug should be promptly discontinued.
3. Insulin
If previous oral medications fail to decrease the fasting plasma glucose below 160 mg/dl or if there is contraindication to use such drugs, then insulin therapy should be prescribed. Short and intermediate acting insulin are favored because in the presence of hepatic dysfunction the half-life of the hormones is prolonged. Dose adjustment is important to avoid hypoglycaemia in patients with chronic liver disease.

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S

tiff socioeconomic improvement has escorts enormous alteration in public health and occurrence of illness in Arab populations. Particularly, chronic non-communicable diseases are taking the place of communicable diseases as the principal foundation of mortality and morbidity. It has become obvious that type-2 diabetes is the result of a collision between thrifty genes and an affluent society of Arab populations, a strong familial aggregation of diabetes and vertical transmission through multiple generations is common.

Diabetes mellitus (DM) is one of the most common non-communicable diseases in the world. Diabetes is a strong genetic and environmental metabolic disorder runs in families. Familial predisposing frequently in type 2 diabetes than in type 1 diabetes. Highly in tribal populations like the Arabs, Pima Indians, Australian aborigines, Asian Indians, Nauruans, Hispanics and Mexican Americans have high familial aggregation and high prevalence of type 2 diabetes.1-7

In Oman, Asfour2 and colleagues have reported that prevalence of diabetes which was 14% in those aged 35-64 years, and in Saudi Arabia, Al-Nuaim and colleagues3 have described the highest crude prevalence rates of diabetes. The prevalence was 34% in the age group 41-59 years. In Bahrain, Al-Mahroos and McKeigue4 have shown that diabetes is among the highest prevalence rates in the world. In 1998 it was estimated that 30% of adults Bahrainis were having type-2 diabetes. Age-standardized prevalence of diabetes was highest 48% in Sunni Arabs, 25% in Jaa-
fari Arabs, and 23% in Iranians. In United Arab Emirates (UAE), El-Mugummer and colleagues5 have illustrated the occurrence of diabetes in native Arabs is related to multifactorial predisposing factors. Obesity, new civilization, lack of activity, as well as consanguinity are strong predictor factors for high prevalence of diabetes among both urban and rural people of Bedouin origin in the UAE. The Shamsi tribal in UAE were positively associated with higher blood glucose levels compared with other tribal groups. Differences in lifestyle between urban and rural residents are becoming blurred with further socioeconomic development and it is expected that the incidence of DM will continue to rise.

In Kuwait, Abdella6 and colleagues have highlighted the pattern of DM among Kuwaiti patients and have provided useful data on the excess risk from moderate hyperglycaemia and other risk factors. They reported that diabetes is a crucial health problem in Kuwait.

Major sociodemographic changes have occurred in Egypt to promote the development of non-communicable diseases. Herman7 and colleagues, have conducted a population-based survey, they found rural areas 4.9% had diabetes, in comparison with urban areas in Cairo were 13.5% had diabetes. Pro- found changes in the way of life of the Arabs during the last 30 years have been associated with the emergence of diabetes. A genetic susceptibility in these populations may explain why diabetes has become an “epidemic”. In comparison to Caucasian and European populations with similar degrees of obesity and glucose tolerance, however Arabs are insulin-resistant prevalent than Europeans. This characteristic, which is a strong predictor of diabetes, seems to be genetically determined in these populations.

The past traditional life-style in Arab populations was characterized by high physical activity and a diet of low energy density. In contrast, for most Arabs, modernized life-style is characterized by reduced physical activity and an energy-dense diet (high in refined carbohydrate and fat) that promotes obesity and maximizes insulin resistance.

In summary, diabetes and its metabolic complications show strong confrontation between ethnic familial thrifty genes and an affluent culture in Arab people. Hence, it is necessary to ascertain the existence of the leading risk factors among new generation young progeny of diabetic parents and risky family’s primitively preventive measures to moderate the incidence of diabetes and consequences complications.

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