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About Diabetes- A Review

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ABSTRACT

Systematic reviews are the building blocks underlying evidence-based practice; they focusattention on the strengths and limits of evidence from research studies about the effectivenessand safety of a clinical intervention. Type 2 diabetes is an increasingly common disease that is closely associatedwith obesity. In 2005, the prevalence of Indians with diagnosed type 2 diabetes was 2.4percent for adults aged 20-39 years, 10 percent for adults aged 40-59 years, and 21 percent foradults aged 60 years or over. From 1980 through 2004, the number of Indians diagnosed withdiabetes more than doubled, from 5.8 million to 14.7 million. Observational studies and clinicaltrials show that improved glycemic control reduces microvascular complications (e.g.,
complications involving the eyes, kidneys, or nerves) and may reduce macrovascular
complications (e.g., heart attack); however, the effects of specific oral diabetes medications onthese outcomes are less certain.
As new classes of medications have become available for the treatment of diabetes, cliniciansand patients have faced a bewildering array of oral medications with different mechanisms ofaction. The first oral diabetes medications were sulfonylureas, which were introduced into themarket in 1955. The second-generation sulfonylureas, which are used today, were introduced in1984. Metformin (a biguanide) was introduced in 1995, meglitinides in 1997, alpha-glucosidase inhibitors in 1998, and thiazolidinediones in 1999.
Generally, clinicians must choose between older, less expensive medications such as a secondgeneration sulfonylurea or metformin and the newer, more expensive medications such as a thiazolidinedione or meglitinide. In addition, clinicians must consider concerns about specificmedications conferring excess cardiovascular risks when compared with other oral diabetesmedications or placebo.

KEYWORDS | Oral medications, risks, obesity, macrovascular complications , insulin,etc.,

Obesity may be responsible for 75% of the problem.Insulin resistance most often goes undiagnosed. Hypertension isanother epidemic, and 75% of such people have diabetes. Highblood cholesterol, and especially triglycerides, are characteristic.

High blood insulin levels also go undiagnosed. Almost one in fourAmerican adults suffer from metabolic syndrome, and will soon bediagnosed with diabetes. Half of all diabetes goes undiagnosed!

According to the Center for Disease Control (CDC) in Atlanta, onein three children born today in the United States will develop type2 diabetes. One in three American children will be diabetic!

Age isone of the biggest factors, since one in four Americans over theage of 65 is diabetic. Stress is also an important factor, and mostWesterners are under a good deal of self imposed stress. No othercountry in the world will approach these statistics. Blacks, Latins,Asians, and Amerindians suffer disproportionately. American Pima

Indians, for example, have an almost 50% rate of outright diabetes.Mexican Pima Indians, on the other hand, follow their traditionaldiet and lifestyle. They have a very low rate of just a few percent.One fourth of adult Navajo Indians are diabetic, according to CDCstatistics. Asian adults in America generally have almost a 40%

rate of diabetes, yet this is rare in the rural areas of Asia. ManyAsian cities have now largely adopted the Western high-fat, highsugar, refined foods diet, and their diabetes rates are soaring. Latinadults in America generally have a 15% diabetes rate, but not intheir native countries. In Papua New Guinea-possibly the leastcivilized country in the world- diabetes is basically unknown.

Black American adults now have a high overall 15% diabetes rate.Yet, this is rare in Africa, where they eat their traditional diet.Caucasian American adults have the lowest overall rate. We are only going to discuss blood sugar metabolism ingeneral, rather than the metabolic syndrome, type 1, type 2, gestational,hypoglycemia, insulin resistance, and other conditions. These are all simply facets of the same basic problem. Diabetes isthe most serious and deadly condition. Currently this is the fifth

leading cause of death in the U.S., and will soon be the fourthleading cause. Almost twenty million Americans now have actualdiabetes, which means about one in every fifteen. In addition, thereare probably about six million more, mostly poor people, who havediabetes, and simply haven't been medically diagnosed. A million

more are newly diagnosed every year. These are mostly theimpoverished and elderly, who can't afford the medical care theyneed. All in all, this would mean about one in twelve Americansare diabetic, with the rates rising every year! This is the fastest

growing disease of all worldwide plain and simple. India andChina are also coping with growing epidemics. In the 1990s thediabetes rate in America increased a full one third. Almost $150billion a year is spent directly and indirectly worldwide on diabetes

treatment. This money is basically wasted on toxic, harmful prescriptiondrugs such as Metformin, Januvia, Onglyza, Amaryl,Avandia, Glucotrol, and Actos. None of these drug therapies areeffective; actually they worsen your health.

The situation gets worse when you consider metabolic

syndrome or Syndrome X. The CDC recently studied 8,814 normalmen and women. They found that 22% of them exhibited at leastthree of the six factors of metabolic syndrome. People over 60,with three of the factors, had a 44% rate, or double the average.This means almost half of Americans over the age of 60 are prediabetic.

This condition is called "pre-diabetes", since such peoplecan plan on becoming diabetic within ten years or less.Again, the basic indications are obesity (especially abdominal),insulin resistance, elevated blood sugar, high cholesterol andtriglycerides,and hypertension. There are three main types of diabetes. Type 1 (insulin dependent) is due to the inability of the betacells in the pancreas to produce insulin. Only 5% to 10% of peoplesuffer from type 1. Surprisingly, Caucasians are more susceptibleto this form. This usually happens in childhood or adolescence.

These patients have to inject insulin, since they can't produce itnaturally. If the pancreas has been removed, or is atrophied, thecondition cannot be cured. Quality of life can be improved immensely,and insulin requirements can be reduced dramatically, byfollowing the advice in this book. Pancreas transplants just don't

work despite the claims. Transplanting a pancreas from a cadaverto a type 1 diabetic requires dangerous anti-rejection drugs, andcauses countless problems. Transplants of just the pancreatic betacells also promise much more than is delivered. Within twenty years science may be able to successfully perform this procedure,but that will merely be allopathic. It will not deal with the cause!

Type 2 diabetics (non-insulin dependent) produce insulin, but the cells simply don't react well to it anymore. This type isvery curable, usually in a year or less). Here, the pancreas not onlyproduces insulin, but usually overproduces it, since the effectivenessis so reduced. The third type is called "gestational diabetes",

since it only affects pregnant women. For some reason,pregnant women are more susceptible to diabetes than anyone else.The best way to understand the dysfunction of insulin andblood sugar is the theory of oxidative stress. Here free radicals run rampant through the body, and use up our antioxidants– glutathione,SOD (superoxide dismutase), beta carotene, vitamin E,vitamin C, CoQ10, melatonin, lipoic acid, and others. This is whyit is so important to, first of all, lower the oxidative stress with better diet and exercise. Secondly, we need to take all the knownantioxidant supplements to neutralize the excess free radicals.These supplements are discussed in detail in chapters six andseven. The high rates of alcohol and nicotine use add to oxidativestress. Coffee (or any form of caffeine) raises blood sugar, and hasother very serious health effects. The scientists of the world are inbasic agreement that free radical oxidative stress is central to bloodsugar conditions.About a half million Americans die every year fromdiabetes. If you are diabetic, you have about three times the rate ofstrokes, about three times the rate of heart attacks, and greatly increased rates of atherosclerosis (clogged arteries). Rememberthat heart disease is the number one cause of death, and the biggestkiller by far. Blindness and vision problems are called "diabeticretinopathy", and are epidemic for people with impaired blood sugar metabolism. Amputation of limbs, due to poor circulation,is common. Various cancers, gastrointestinal infections,osteoporosis, erectile dysfunction, poorly healing wounds, kidneyinfections and failure, poor sleep, are all part and parcel here.

Psychology is affected including depression, senility, Alzheimers, impaired memory, and other problems. Any blood sugar dysfunctionmeans poor quality of life and early death. The pancreasdeteriorates, nerve damage of various kinds can be expected, liver

disease is routine, and skin infections (especially Staphylococcus) are common. Your liver is central here since it produces the bloodsugar from the food you eat. Your kidneys are the second mostimportant organs. The list of side effects is almost endless, sincethe total health of the body is destroyed. If you have type 1 diabetes, pancreas transplants and betacell (the insulin producing pancreatic cells) transplants just don'twork at all. You can dramtically reduce your insulin requirements, reduce your medication, and improve your health immensely, withthe information in this book. Even if your pancreas has beenremoved, or atrophied beyond repair, you can still live a good lifewith minimal insulin. Anyone with type 2 diabetes can cure themselves within a year, and live a normal, healthy life.

1. Definition

1.1. Diabetes mellitus describes several syndromes of abnormal carbohydrate metabolism that are characterised by hyperglycaemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of resistance to the action of insulin.

1.2. Type 1 diabetes (T1DM). Previously known as insulin-dependent (IDDM) or juvenile-onset diabetes. It is characterised by an autoimmune-mediated destruction of the pancreatic beta cells that are responsible for the production of insulin, leading to an absolute deficiency of insulin.

1.3. Type 2 diabetes (T2DM). Previously known as non-insulin-dependent (NIDDM), maturity-onset, or adult-onset diabetes. It is, by far, the most common type of diabetes (~90%) and is characterised by varying degrees of resistance to the action of insulin with relative insulin deficiency. It is a progressive disorder with decreasing ability to produce insulin over time, leading to increased therapeutic requirements.

1.4. Diabetes mellitus can arise as a feature of various diseases, genetic or acquired, referred to collectively as secondary diabetes.

1.5. Genetic causes of secondary diabetes. There are a large number of genetic syndromes associated with the development of diabetes, although collectively these account for probably only 1-2% of the total number of cases of diabetes.

1.6. Acquired causes of secondary diabetes

1.6.1. Pancreatic disease. The pancreas is responsible for production and release of insulin and therefore any disease that destroys pancreatic tissue can result in diabetes.

Haemochromatosis. A genetic condition characterised by excessive iron deposition in various organs of the body, including the pancreas. Diabetes affects around 50% of people with this condition

Cystic fibrosis. Diabetes usually arises in the late teens or early twenties

Acute or chronic pancreatitis. Inflammation and destruction of the pancreas, secondary to alcohol or gallstones, can lead to diabetes

Pancreatic cancer
Pancreatic surgery

1.6.2. Endocrine disease. Any endocrine condition where there is excessive production of a hormone that opposes the action of insulin, i.e. increases glucose levels, can cause diabetes.

Hyperthyroidism (excess thyroid hormone production)

Acromegaly (excess growth hormone production)Cushing's syndrome (excess cortisol production)

1.6.3. Drugs. There are a large number of drugs that cause or worsen diabetes.

Glucocorticoids, which are used in conditions such as chronic lung disease, rheumatoid arthritis, inflammatory bowel disease and polymyalgia rheumatica Drugs used to lower blood pressure: diuretics, (mainly thiazide diuretics), β-blockers Drugs used to treat HIV infection

1.7. Treatment of secondary diabetes is the same as for type 1 or type 2 diabetes, depending on severity i.e. insulin or oral medication, although the underlying cause should also be treated.

3. Aetiology

3.1. Type 1 and type 2 diabetes are very distinct diseases in terms of the underlying aetiology.

3.2. Type 1 diabetes

3.2.1. T1DM is an autoimmune disorder, resulting in the destruction of the β-cells in the islets of Langerhans, areas of endocrine tissue within the pancreas.

3.2.2. The lifetime risk of developing diabetes is greatly increased when another member of the family has T1DM (6% risk in a child if a parent has T1DM, 5% risk in a brother/sister, and 30% risk in an identical twin).

3.2.3. Environmental factors most likely trigger the onset of diabetes in genetically predisposed individuals. The process progresses over months or years and T1DM occurs when approximately 60% of the β-cells have been destroyed.

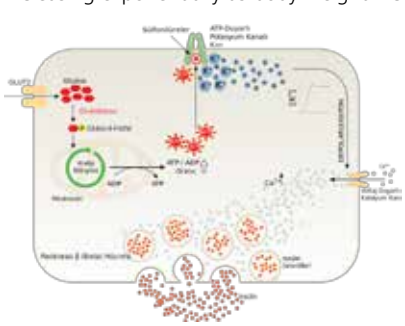
3.2.4. Evidence for an environmental trigger for the onset of diabetes is based on epidemiological research. For example, people who have migrated from an area of low incidence of T1DM to an area of high risk, adopt the same risk as the population to which they move. The most commonly associated factors are viruses (e.g. Coxsackie B virus), various food components (e.g. cow's milk and wheat proteins), and low exposure to sunlight. There is no direct evidence to support a cause and effect but only to suggest a possible association between these factors and the development of diabetes.

3.3. Type 2 diabetes

3.3.1. T2DM develops due to a combination of insulin resistance (the body's inability to respond to the glucose lowering effects of insulin) and a decreased ability of the β-cells to produce insulin. Whilst the β-cells are able to meet the insulin secretory demand, normal glucose levels can be maintained but as β-cell function declines, progressive hyperglycaemia ensues. In the early stages it is often postprandial glucose levels that are most abnormal.

3.3.2. T2DM has a genetic component: 10% of patients with T2DM will have an affected brother/sister. However, the genetics are much more complex than in T1DM.

3.3.3. Environmental influences have a significant role in the development of T2DM. The main risk factors for developing T2DM are reduced physical activity and obesity, with the risk increasing exponentially as body weight increases.



Medications

Many anti-hyperglycemic drugs are available to help patients with type 2 diabetes control their blood sugar levels. Most of these drugs are aimed at using or increasing sensitivity to the patient's own natural stores of insulin.

For the most part older oral hypoglycemi drugs -- particularly metformin -- are less expensive than, and work as well as, newer diabetes drugs. They are generally recommended as first-line drugs to use. Metformin is a safe and effective drug because it does not cause weight gain or too-low blood sugar. Metformin can also help lower LDL ("bad") cholesterol.

In general, these drugs will reduce hemoglobin A1C levels by 1 - 2%. Adding a second oral hypoglycemic is usually recommended if inadequate control is not achieved with the first medication. For the most part, doctors should add a second drug rather than trying to push the first drug dosage to the highest levels[21][22].

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors, including acarbose (Precose, Glucobay) and miglitol (Glyset), reduce glucose levels by interfering with the absorption of starch in the small intestine. Acarbose tends to lower insulin levels after meals, a particular advantage, since higher levels of insulin after meals are associated with an increased risk for heart disease. Some evidence suggests that early use of these drugs may reduce heart risk factors, including high blood pressure. Alpha-glucosidase inhibitors are not as effective alone as other single oral drugs, but combinations, such as with metformin, insulin, or a sulfonylurea, increase their effectiveness.

Side Effects:-These medications need to be taken with meals. Unfortunately, about a third of patients stop taking the drug because of flatulence and diarrhea, particularly after high-carbohydrate meals. The drug may also interfere with iron absorption.

Alpha-glucosidase inhibitors do not cause hypoglycemia when used alone, but combinations with other drugs do. In such cases, it is important that the patient receive a solution that contains glucose or lactose, not table sugar. This is because acarbose inhibits the breakdown of complex sugar and starches, which includes table sugar.

GLP-1 Inhibitors (Exenatide)

Incretinmimetics belong to a new class of drugs that help improve blood sugar control. Incretins include glucagon-like peptide-1 (GLP-1) inhibitors and DDP-4 inhibitors.

In 2005, the FDA approved exenatide (Byetta), the first GLP-1 inhibitor drug. Exenatide is an injectable drug that is a synthetic version of the hormone found in the saliva of the Gila monster, a venomous desert lizard. Exenatide is injected twice a day, 1 hour before morning and evening meals. It is prescribed for patients with type 2 diabetes who have not been able to control their glucose with metformin or a sulfonylurea drug. It can be taken in combination with these drugs or alone.

Side Effects:-Exenatide stimulates insulin secretion only when blood sugar levels are high and so has less risk for causing low blood sugar (hypoglycemia) when it is taken alone. However, the risk for hypoglycemia increases when exenatide is taken along with a sulfonylurea drug. There does not appear to be a risk for hypoglycemia when exenatide is used along with metformin. Other side effects may include nausea, vomiting, and diarrhea.

Exenatide has been associated with cases of acute pancreatitis, which is sudden inflammation of the pancreas. Symptoms of acute pancreatitis include severe abdominal pain that may radiate to the back. The pain may or may not be accompanied by nausea and vomiting. Patients who feel severe stomach pain that does not go away should seek prompt medical

attention. In rare cases, exenatide has been associated with hemorrhagic and necrotizing pancreatitis, which can potentially be life threatening.

DPP-4 Inhibitors (Gliptins)
Dipeptidyl peptidase-4 (DPP-4) inhibitors, also called gliptins, are the second class of incretin drugs. In October 2006, the FDA approved the first DPP-4 inhibitor. sitagliptin (Januvia). It can be used alone or in combination with metformin or a thiazolidinedione drug. It may also be used as add-on therapy to a sulfonylurea drug. In 2007, the FDA approved Janumet, which combines sitagliptin with metformin in one pill. Other DPP-4 drugs being studied include vildagliptin (Galvus) and saxagliptin.

DPP-4 inhibitors work in a similar way to GLP-1 inhibitors. However, unlike exenatide, which is given by injection, DPP-4 inhibitor drugs are taken as pills by mouth.

Like exenatide, DPP-4 inhibitors do not cause weight gain, have low risks for hypoglycemia, and have few severe side effects. The most common side effects include upper respiratory tract infection, sore throat, and diarrhea.

Pramlintide (Symlin)
Approved in 2005, pramlintide (Symlin) is a new type of injectable drug that may help patients who take insulin but still need better blood sugar control. Pramlintide is a synthetic form of amylin, a hormone that is related to insulin. Pramlintide is used in combination with insulin to lower blood sugar levels in the 3 hours after meals.

Insulin Replacement
Insulin replacement may be necessary when natural insulin reserves are depleted. It is typically started in combination with an oral drug (usually metformin).

Because type 2 diabetes is progressive, many patients eventually need insulin. However, when a single oral drug fails to control blood sugar it is not clear whether it is better to add insulin replacement or a second or third oral drug.

Some doctors advocate using insulin as early as possible for optimal control. However, in patients who still have insulin reserves, there is concern that extra natural insulinwill have adverse effects. Low blood sugar (hypoglycemia)and weight gain are the main side effects of insulin therapy. It is still not clear if insulin replacement improves survival rates compared to oral drugs, notably metformin.

Fortunately, studies to date have not reported any adverse cardiac effects in patients with type 2 diabetes who take insulin. In fact, insulin has been associated, in some cases, with improvement in heart risk factors. More research is needed to clarify these important issues.

Table:- 1

Comparison of anti-diabetic medication			
agent	mechanism	advantages	disadvantages
Sulfonylurea (glyburide, glimepiride, glipizide)	Stimulating insulin release by pancreatic beta cells by inhibiting the K_{ATP} channel	Inexpensive Fast onset of action No effect on blood pressure No effect on low-density lipoprotein lower risk of gastrointestinal problems than with metformin more convenient dosing	causes an average of 5–10 pounds weight gain Increased risk of hypoglycemia Glyburide has increases risk of hypoglycemia slightly more as compared with glimepiride and glipizide Higher risk of death compared with metformin
Metformin	Acts on liver to cause decrease in insulin resistance	not associated with weight gain low risk of hypoglycemia as compared to alternatives Good effect on LDL cholesterol Decreases triglycerides no effect on blood pressure inexpensive	increased risk of gastrointestinal problems Contraindicated for people with moderate or severe kidney disease or heart failure because of risk of lactic acidosis increased risk of Vitamin B12 deficiency less convenient dosing Metallic taste
Alpha-glucosidaseinhibitor (acarbose, miglitol, voglibose)	Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates	slightly decreased risk of hypoglycemia as compared to sulfonylurea not associated with weight gain decreases triglycerides no effect on cholesterol	less effective than most other diabetes pills in decreasing glycatedhemoglobin increased risk of GI problems than other diabetes pills except metformin inconvenient dosing expensive
Thiazolidinediones (Pioglitazone, Rosiglitazone)	Reduce insulin resistance by activating PPAR-γ in fat and muscle	Lower risk of hypoglycemia Slight increase in high-density lipoprotein Actos linked to decreased triglycerides Convenient dosing	increased risk of heart failure causes an average of 5–10 pounds weight gain associated with higher risk of edema associated with higher risk of anemia increases low-density lipoprotein Avandia linked to increased triglycerides and risk of heart attack Actos linked to increased risk of bladder cancer slower onset of action requires monitoring for hepatoxicity associated with increased risk of limb fractures expensive

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

Table:-2

Oral anti-diabetic drugs and Insulin analogs (A10)			
Insulin[33]		Sensitizers	• Metformin# • Buformin‡ • Phenformin‡
		TZDs/" glitazones" (PPAR)	• Pioglitazone • Rivoglitazone† • Rosiglitazone • Troglitazone
	Sensitizers	Dual PPAR agonists	• Aleglitazar[34] • Muraglitazar[35] • Saroglitazar[34] • Tesaglitazar§
Insulin[33]			• 1st generation: Acetohexamide • Carbutamide • Chlorpropamide • Metahexamide • Tolbutamide • Tolazamide
		Sulfonylureas	2nd generation: Glibenclamide (Glyburide)#
Secretagogues	K+ ATP		• Glibornuride • Glipizide • Gliquidone • Glisoxepide • Glyclopyramide • Glimepiride • Gliclazide
		Meglitinides/" glinides	• Nateglinide • Repaglinide • Mitiglinide
		• Exenatide • Liraglutide	

MECHANISM OF ACTION

Human studies indicate that the hypoglycemic effect of salicylatesis mediated, at least in part, by enhanced insulin secretion.Since salicylates inhibit prostaglandin synthesis in avariety of tissues,58 it has been proposed that a similar actionoccurs in the pancreatic beta-cell, and that this inhibition isrelated to enhanced glucose-induced insulin secretion.59 Themost convincing evidence supporting this contention comes

from a study using sodium salicylate in monolayer cultures ofneonatal rat pancreases. Using this model, Metz and coworkersdemonstrated concomitant enhanced insulin secretionand diminished prostaglandin E synthesis.60 In man, theonly species in which salicylates have repeatedly been shownto be insulinogenic, there is indirect evidence supportingthis contention. In normal man, infusions of prostaglandinE2 and a methylated E2 analogue inhibit the acute insulin responseto a glucose pulse,22'61"63 while, as noted, salicylatesenhance the acute insulin response in both normal and diabeticsubjects.20'22 In addition, the infusion of lysine acetylsalicylate

innormals reverses and also augments the glucoseinducedacute insulin response blunted by furosemide, astimulator of endogenous PGE synthesis.64 On the other

hand, Spellacy and co-workers, studying nondiabeticthirdtrimesterpregnant women and using substantially lowerdoses of PGE2 compared with those used by others,22'61 63found no change in either glucose or insulin levels.65

The interrelationship between salicylates and insulin secretionhas been further refined by Robertson and his colleagues. In normals, they have demonstrated that the glucose-

induced acute insulin response inhibited by an infusionof epinephrine is partially restored by the concomitant infusionof sodium salicylate, a finding consistent with the hypothesisthat endogenous PGE synthesis mediates alpha-adrenergic

inhibition of insulin secretion.66"69Observations in diabetic subjects in whom salicylateslower blood glucose with either a decrement or eliminationof the insulin dose,4"7 and in animals in which salicylateslower glucose without concomitant increases in insulin secretion,40'50 suggest that the hypoglycemic effect of salicylates

may also be mediated by mechanisms other than enhancedinsulin secretion.

What might these mechanisms be? In the laboratory animaland under appropriate conditions, salicylates have a glycogenolyticeffect in liver28'31*32'34'70 and in muscle.71"73These relatively transient effects are difficult to reconcilewith the long-term dimunition of blood glucose seen inman.6 Furthermore, in man, salicylates appear to have littleeffect on glycogen metabolism, as evidenced by a normal responseto glucagon in aspirin-treated subjects.6 Recently,Woods and associates have demonstrated in the perfused ratliver that sodium salicylate inhibits gluconeogenesis fromtwo major glucose precursors, lactate and alanine,74 and

have suggested that this effect may be due to the uncouplingof oxidative phosphorylation75 and to the inhibition of theenzyme alanine aminotransferase. In addition, others havereported aspirin-induced inhibition of gluconeogenesis in incubatedrat slices but enhanced gluconeogenesis in renal tissue.'

A salicylate-induced inhibition of intestinal glucose absorptionappears unlikely because aspirin does not interferewith glucose absorption in man,4 although contradictoryfindings have been reported with animal preparations.77'78

Another possibility is that salicylates may stimulate basalmetabolic rate (BMR) and thus cause a lowering of bloodglucose. This hypothesis finds support in the observations ofReid et al.4 but not in those of other workers.8'42 Additional

evidence against this possibility has been found in studies inwhich the hypoglycemic effect of 2:4 dinitrophenol (DNP)and aspirin, both administered to diabetic subjects to producecomparable increases in BMR, was compared.79 In thiscase, aspirin had a substantially greater hypoglycemic effectthan DNP, suggesting that enhanced BMR is not responsiblefor the fall in blood sugar.

It appears possible that the glucose lowering action of aspirinmay be mediated by an enhanced peripheral glucose uptakeindependent of any insulinogenic effect. However, evidencefrom in vitro studies is confusing and contradictory,and from human studies lacks definitiveness.. Studies on isolatedmuscle tissue derived from normal rats have shown thatsalicylates enhanced,80 inhibited,71'73 or had no effect on theuptake of glucose.71>73>81 Despite assertions that differencesof media composition are responsible for these discrepancies,80'82 various investigators using the same media havefound different effects, for reasons that are obscure. With abicarbonate buffer, Manchester and his associates80 foundenhanced glucose uptake, whereas Segal and co-workers81and Huggins and Smith73 found no effect. Using a phosphate

buffer, Smith and Jeffrey71 observed, depending on thelength of time of incubation, both no effect and inhibitionby salicylate on glucose uptake, while Huggins and Smith73observed inhibition. In patients with mild diabetes, Stowersand co-workers83 found that salicylates given during glucoseloading enhanced glucose capillary-venous difference, a findingconsistent with increased peripheral uptake. In addition,changes in other metabolic parameters, including serumpyruvate, lactate, potassium, and inorganic phosphate, wereconsistent with such an effect. However, insulin levels werenot measured in this study, leaving doubt regarding the

possible

role of the hormone in the observed changes. Perhapsthe most convincing evidence suggesting a direct salicylateinducedstimulation of peripheral glucose uptake came fromLinbeck and his associates,84 who induced clinical hypoglycemia,without augmentation of insulin levels, by the oraladministration of aspirin to an infant.

Health Day News September 26, 2013

Diabetes patients who take drugs called sulfonylureas as an initial therapy have a higher risk of death than those who take the diabetes drug metformin, a new study says.

The British researchers said the findings suggest that it may no longer be appropriate to offer sulfonylureas as a first-line treatment.

Diabetes experts in the United States agreed that the study could have an impact on care.

The findings "will change the practice of glucose [blood sugar]-lowering therapy," said Dr. Spyros Mezitis, an endocrinologist at Lenox Hill Hospital in New York City.

But he added that "more study is need to confirm this data," and use of the alternative drug, metformin, is not always the answer. "Metformin and other oral hypoglycemic agents have their drawbacks, and probably we will see earlier use of insulin in type 2 diabetics," Mezitis said.