DECREASING RISK IN DM

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Under-appreciated Risk of DM

Diabetes mellitus (DM) is reaching epidemic proportions in the U.S. The number of diagnosed patients has increased steadily over the past four decades. The total number of people afflicted with DM, including those who remain undiagnosed, is estimated at about 15 million. That number is expected to reach 23 million by the year 2025. It has an enormous impact on morbidity and mortality.

This issue of *Heartbeat* will present the latest treatments for DM and insulin resistance, and data that support the link between the vessel wall, clinical events and protection from the clinical event, in patients with this disease.

DM is an important, but greatly undervalued, risk factor for cardiovascular disease (CVD). We have long known that diabetes imparts risk, but we really don't recognize the magnitude of that risk. Eighty percent of diabetics die as a result of CVD, and up to 50% have significant atherosclerotic disease at the time of initial diagnosis. Once people with DM develop CVD or heart failure (HF), their outcomes are worse than those in people without diabetes.

It is our view and that of many others that a diabetic without overt vascular disease should be evaluated and treated as if vascular disease was present. Clinical trial data show that the risk of a diabetic without vascular disease is comparable to that of a non-diabetic who has had a CV event[1].

It is known that patients with diabetes, particularly women, exhibit an increased risk for coronary events, including angina, strokes,

claudication, HF, myocardial infarction (MI) and sudden death. Patients with DM have an estimated two to five-fold increased risk of developing atherosclerotic CVD[2 3].

Insulin Resistance

This enhanced risk was previously thought to arise primarily from hyperglycemia and related glycosylated products. Insulin resistance appears to be the cardinal feature of the cardiovascular dysmetabolic syndrome (CDS) and greatly influences the development of type 2 DM, hypertension, dyslipidemia and CVD. Insulin resistance antecedes frank, overt diabetes by years if not decades and it alone, even without DM, greatly increases risk of atherosclerosis. Hyperinsulinemia, a hallmark of insulin resistance, is an independent risk factor for CVD and is associated with a higher risk of hypertension (2-fold), hypertriglyceridemia (3-4-fold), and type 2 DM (5-6-fold), as well as low levels of high-density lipoprotein-cholesterol (HDL-C)[4]. The "insulin resistance syndrome" or CDS is usually associated with other risk factors (obesity, hypertension, dyslipidemia, and hyperglycemia) and is diagnosed by the presence of at least two components[5]. (See Table pg. 2)

Endothelial Dysfunction (ED)

CDS produces a cascade of events that precipitate endothelial dysfunction (ED), which is the first step in the atherosclerotic process[6 7]. The

endothelium of the vessel wall is involved in maintaining lumen size and vessel cell growth,

Cardiovascular dysmetabolic syndrome (CDS)

Diagnostic criteria:

- Dyslipidemia
  - decreased HDL-C < 40mg/dl or
  - increased triglycerides > 140 mg/dl
- Insulin resistance (hyperinsulinemia)
  - Type 2 DM or
  - Fasting plasma glucose ≥ 110 mg/dl
- Obesity ("apple" body configuration)
  - Body mass index > 25 kg/m^2 or
  - Waist > 100 cm (39 in)
- High blood pressure
  - SBP ≥ 140 mm Hg or
  - DBP ≥ 90 mm Hg

or type 2 DM, there is an increase in release of vasoconstrictors, particularly endothelin I and thromboxanes, whereas there is a deficiency of vasodilators, particularly nitric oxide. Nitric oxide is also a very potent inhibitor of vascular smooth muscle cell (VSMC) growth. This can result in increased thickness of the intima-media. In general, patients with insulin resistance also have decreased fibrinolytic activity and higher levels of plasminogen activator inhibitor (PAI-1) exposing lumen walls of vessels to recurrent thrombi. This sets the stage for the beginning and progression of the atherosclerotic process resulting in acute events[8].

Glucose Control

We have data from the United Kingdom Prospective Diabetic Study (UKPDS)[9], showing that tight glycemic control (HbA_{1c} ≤ 7%) decreases microvascular complications. The macrovascular endpoints were reduced in the intensive group but did not reach statistical significance, perhaps because 10 years' follow-up is too short to find changes in atheroma or because drugs like thiazolidinediones (which target insulin resistance) were not used.

Treatment Considerations

Type 2 DM is a combination of increased insulin resistance, increased hepatic glucose production and impaired insulin secretion, which leads to hyperglycemia. Sulfonylureas (SUs), which augment insulin secretion, have been the traditional choice; however, about 20-30% have poor initial response (primary failure)[10]. The secondary failure rate is about 5-10% per year and after about 10 years most patients require a second agent[11]. This *Heartbeat* will focus on the benefits of two of the five classes of oral agents approved for the treatment of type 2 DM:

- Biguanides (Glucophage)
- Thiazolidinediones (glitazones)
  - Actos [pioglitazone]
  - Avandia [rosiglitazone]
  - Rezulin [troglitazone]

Glucophage is as effective as SUs but does not appear to be associated with weight gain, as do all other oral agents, and rarely causes hypoglycemia, which may be associated with SU use. It decreases hepatic glucose output (major action), intestinal glucose absorption and increases peripheral uptake and utilization of glucose. In the UKPDS[12], Glucophage was compared to conventional treatment (diet) in overweight patients for 10.7 years for glycemic control. A net reduction for MI, stroke, and death was shown with Glucophage. Lactic acidosis, a rare but serious side effect of Glucophage usage, can be minimized by avoiding use in patients with diseases known to cause lactic acidosis, such as renal dysfunction or HF[13].

The **glitazones** are an option for combination therapy for those patients who fail to maintain adequate glucose control with SUs or Glucophage[14]. This class is also effective as mono-therapy through the insulin sensitizing and decreased hepatic glucose output effects, to reduce both glycosylated hemoglobin and fasting blood sugars. The glitazones effectively and significantly reduced hyperinsulinemia[15] and have various effects on lipoprotein patterns (mostly beneficial) and additional antiatherogenic effects (improving ED).

1. Improvement of the lipid profile
   - ♦ Increase HDL-C
   - ♦ Decrease triglycerides
   - ♦ Increase total LDL-C but decrease small dense LDL-C (more atherogenic) while increasing large buoyant LDL-C (less atherogenic) only shown with troglitazone[16]
2. Decrease PAI-1 levels which improve fibrinolytic activity[17]
3. Inhibit growth and migration of VSMCs
4. Inhibit thrombin induced platelet aggregation[18]
5. Promote more normal vasodilatory response
6. Decrease peripheral vascular resistance (decreased blood pressure)
7. Decrease insulin resistance and reduce the risk of developing type 2 DM

The potential correction of these conditions, which are usually present in those with insulin resistance, could help avert atherosclerotic progression and help prevent the occurrence of acute coronary events.

Control of Hypertension

We have data from two very recent and good hypertension trials, the UKPDS[19] and the HOT[20] trial, that show that diabetics do very well with aggressive anti-hypertensive therapy. Coronary risk is markedly reduced when blood pressure is lowered to normal (<130/80 mm Hg with goal of 120/80 mm Hg).

Lipid Control

There is also data from 4S[21], CARE[22], and LIPID[23] that show that the diabetic treated with statins to reduce LDL-C reduces his or her CV risk almost to that of the non-diabetic placebo individuals. Most recently, data from VA-HIT[24] showed that gemfibrozil increased HDL-C and decreased triglycerides (the usual abnormal profile seen in type 2 DM or CDS) resulting in decreased mortality and coronary events, and slowing of disease progression.

Conclusions/Recommendations:

1. DM is a big, big story. It really belongs in a special category, the most important neglected major CV risk factor, often assessed but under-appreciated. DM has been sort of an "orphan," belonging neither to the AHA or the NHLBI. It was considered the endocrinologist's problem. The evidence is now overwhelming that it is a shared problem for both cardiologists and endocrinologists. We now are not only worrying about controlling glucose but also treating all of the associated CV risk factors. We realize that heart disease and stroke are the most common causes of death in diabetics.
2. Insulin resistance (CDS) alone, without overt diabetes (glucose $\geq$ 126 mg/dl) greatly increases risk for atherosclerosis through a very early and marked impact on endothelial function (the vascular connection).
3. We now have to identify and target insulin resistance to improve glucose control using insulin -sensitizers (Glucophage and/or preferably glitazones), that may further help delay the onset of diabetes-related complications.
4. Accumulating data indicate beneficial effects of treating CDS, with the glitazones, on the numerous CV risk factors and even

preventing the development of type 2 DM by improving and/or preventing ED. The glitazones, which can be used as an add-on in combination therapy appear to be moving into the role of drug of first choice for glucose control because of their other non-glucose lowering beneficial effects such as:

- ♦ decreasing blood pressure
- ♦ improving lipid profiles
- ♦ decreasing thrombotic risk
- ♦ potential benefit in acute coronary syndromes

5. The experts consider all three glitazones as a class, and all require baseline liver function testing followed by regular monitoring to check for possible idiosyncratic hepatotoxicity.
6. Aggressively control hypertension (<130/80 with a goal of 120/80), always using an ACE inhibitor as part of the program. This treatment will significantly decrease CV risk, renal complications and improve outcomes.
7. Aggressively control all lipid abnormalities with the following order of priorities:
   - ♦ Lower LDL-C to <100 mg/dl
   - ♦ Raise HDL-C to >45 mg/dl
   - ♦ Lower triglycerides to <150 mg/dl
   - ♦ Treat combined hyperlipidemia using high dose statins as the first choice and statins plus gemfibrozil as the second choice

   These treatments decrease CV risk and mortality. Glucose control and behavioral interventions like diet, weight loss, exercise, and smoking cessation are an integral part of treating all dyslipidemias and DM.
8. All middle-aged and older diabetics should take an aspirin to decrease CV events as recommended per the ADA.

The key point of this *Heartbeat* is that we not only want to treat a high glucose, but more importantly, we have to treat the significant CV risk of the diabetic patient too! Diabetic patients die mainly of MI's and stroke.

Improved outcomes (decreased MI's and strokes) have been documented by treating diabetics with
ASPIRIN, STATINS, and ACE INHIBITORS[25] [26]. The evidence is mounting that these medications improve ED, the common denominator of increased CV risk, and they should be considered for every diabetic patient unless contraindicated. Treatment of CDS and type 2 DM with glitazones improves glucose control but also addresses hypertension, dyslipidemia, and (ED), which all lead to CV complications. Perhaps one of the *glitazones* should also be part of every diabetic treatment program.

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