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Reducing CV Risk of MetS & T2DM—Part 1

Diabetes (T2DM) is a huge risk factor for cardiovascular disease (CVD) and is considered a coronary artery disease (CAD) equivalent. The leading cause of death for people with T2DM is CVD. The CVD risk associated with metabolic syndrome (MetS), a pre-diabetic state, is about two times higher than the general population, and with progression to T2DM, the risk increases to about four times higher.

A good way to measure the severity of CV risk in a patient with T2DM is to consider it equivalent to that of a person without T2DM with a low-density lipoprotein cholesterol (LDL-C) level approximately twice as high. This is consistent with clinical trial experience. Patients with T2DM in statin trials who receive the active treatment have a higher event rate than patients without T2DM who are given the placebo. This shows that patients with T2DM, even if they are taking a statin, have very high residual risk. So this population needs much more risk factor modification, in addition to statin therapy, to treat that residual risk.

The next two *Heartbeats* will outline a very aggressive plan to both prevent and treat MetS and T2DM and their associated very high CV risk, based on the most recent data. This issue will cover treatment of MetS and prevention of diabetes. Next month's issue will cover T2DM.

MetS

It has been estimated that atherosclerosis accounts for approximately 65% of diabetic mortality: 40% due to ischemic heart disease, 15% due to other CVD, and 10% due to cerebrovascular disease.[1] Thus, macrovascular disease represents the number 1, 2, and 3 problem faced by type 2 diabetics. The glucose rise is the last step in the evolution of the pathophysiology of T2DM. ***Therefore, when a patient presents with fasting hyperglycemia (> 126mg/dL) and you diagnose diabetes, you should realize that the patient has been exposed to this abnormal metabolic milieu for 10 to 12 years, and your treatment is years behind—thus our aggressive stance.***

Obviously, the first goal will be to identify and diagnose MetS in order to treat and prevent T2DM and the increased CVD risk. MetS is a constellation of major risk factors for CVD which include insulin resistance with or without hyperglycemia, abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, low HDL-C and small LDL-C particles), high blood pressure and prothrombotic and pro-inflammatory states. Diagnostic criteria are outlined below (Table 1).

Table I. NCEP Clinical ID of the Metabolic Syndrome*

Risk factor	Defining Level
Abdominal Obesity	Waist Circumference
Men	>40 in
Women	>35 in
Triglycerides (TG)	≥ 150mg/dL
HDL –C	
Men	<40mg/dL
Women	<50mg/dL
Blood pressure	≥130/≥85mmHg
Fasting glucose	≥ 100mg/dL

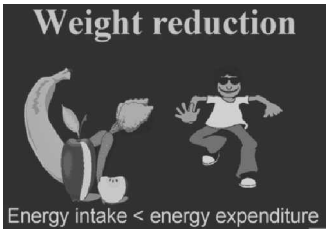
*Diagnosis is dependent on 3 or more factors

Prevalence

The “double whammy” of the aging of the population and the dangerous increase in inactivity and obesity in younger people threatens to bring about an epidemic of CVD greater than previously imagined. This epidemic is linked to a dramatic increase in the prevalence of T2DM, which is expected to double within the next 25 years. Approximately 47 million Americans—about 1 in 4 adults (23%)—have MetS. This figure includes 10 - 15 million people with T2DM. Incidence of MetS in adults is comparable to that of hypertension (24%). As the US population ages, its prevalence will increase steadily among men and women in the older age groups. Prevalence among older segments of the population is already approaching 50%.[2]

Treatment:

Therapeutic lifestyle change (TLC) is a key therapeutic objective. All components of MetS are positively affected by weight loss and exercise. TLC includes dietary modifications, increased physical activity, and weight control. Patients should meet with a registered dietician initially to discuss their necessary dietary modifications.



Even modest weight reductions, in the range of 5% to 10% of initial body weight, are associated with significant clinical improvement. *Successful weight loss requires that more energy be expended than consumed on a daily basis.*

Weight Reduction: Studies with formula diets of widely varying composition have shown that all energy-restricted diets reduce weight and improve glycemic control, lipids and blood pressure. The basis for optimizing CV health for individuals is an overall diet that emphasizes vegetables, fruits, whole grains, fish, and low-fat dairy products, along with regular physical activity. We emphasize that diet—a four letter word—is out of vogue and that a change in habits is the new order.

The first step is to convert the patient from "Western" habits to "Prudent" habits (Table 2).[3] This will result in a 60% less chance of developing T2DM.

Table 3. "Western" Vs "Prudent" Habits

Western Habits	**Prudent Habits**
Red meat	Vegetables
Processed meat	Fruit
French fries	Fish
High-fat dairy products	Poultry
Refined grains—“white carbos”	Whole grains./ carbos in moderation
White rice /potatoes	
Sweets & desserts	

Exercise: There is consensus that virtually all individuals can benefit from regular physical activity—minimum of 30 minutes 5x/week. Although physical activity and exercise are key factors in successful weight reduction programs, the effects are considerably less dramatic than caloric restriction. Regular exercise has also been shown to facilitate maintenance of weight loss because of increased catabolism at 12 weeks. Recent research indicates that men who added exercise to dieting had better discipline and decreased hunger.[4] They also lost more weight than those who dieted without exercise.

An exercise program of moderate physical activity, if undertaken regularly by overweight and obese individuals, can increase maximal oxygen uptake and thus cardiorespiratory fitness—which by itself decreases risk—“survival of the fittest.”[5] When beginning an exercise program, patients should start slowly and gradually increase to 30-45 minutes/day, minimum 5 days/week (150 minutes), preferably daily. A minimum of 30 minutes of physical activity of moderate intensity, e.g. brisk walking (>/=3 mph), almost every day is associated with decreases in blood pressure and lipids. More recent recommendations favor 60

minutes of physical activity daily along with the addition of resistance training three times a week. The benefits of exercise in glycemic control are independent of weight loss.[6] Mechanisms of cardiovascular protection include decreased inflammation, improved early diastolic filling, improved endothelial function, and reduced abdominal fat. TLC is a key determinate for successfully reversing the pathophysiology of MetS through the long-term maintenance of weight loss and fitness—thus preventing or ameliorating CVD and T2DM.

TLC works. In the Finnish Diabetic Prevention Study, (TLC vs. no change) the 58% reduction in the development of T2DM (23% vs 11% absolute rates) was particularly striking.[7] In a new follow-up study 3 years after the end of the study, those in the intervention group still had a reduced incidence of T2DM.[8] In the US Diabetic Prevention Study (US DPS) the 58% reduction in the development of T2DM was reproduced comparing TLC to placebo.[9]

Medication: In another arm of US DPS (metformin vs placebo), development of T2DM was decreased by 31% with metformin. In the recently released Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone reduced the risk of diabetes by 60%.[10] Despite this impressive reduction in progression to T2DM, some concern remains about possible side effects (weight gain and heart failure), little data on the long-term benefits and the high cost of rosiglitazone. Metformin is still competitive as the drug of choice for prevention of T2DM because of proven CV risk reduction and lower cost.[11] Metformin is not usually associated with weight gain and sometimes is associated with weight loss.

Beyond TLC and metformin or a glitazone, treatment of all traditional CVD risk factors is extremely important and will have an impressive impact on morbidity and mortality in subjects with MetS. All of these patients should be on baby aspirin—to help reverse the prothrombotic state and lipid-lowering therapy to obtain an optional LDL-C goal of < 100mg/dL and a non-HDL-C goal of < 130mg/dL minimum because of their excessive associated risk. Patients with MetS and T2DM frequently have a triglyceride/HDL-C (TG/HDL) axis disorder in which TGs are high and HDL-C is low. In these patients LDL-C is not the best surrogate for ApoB, the real lipid culprit invading the vascular wall. So, it's important to get non-HDL-C, a better ApoB surrogate, to goal when TGs are > 200mg/dl.[12] TGs > 500mg/dl should be treated first with fibrates or niacin before attempting to reach LDL-C goals with statins. These recommendations follow American Heart Association and NCEP III guidelines. There are no NCEP targets for HDL-C and TG. The ADA has a different approach, recommending treatment of TG > 150 and HDL-C < 40. Fenofibrates are preferred in combination with statins (and ezetimibe) as needed. Combination therapy is usually needed for combined lipid disorders. However, no outcomes or safety data are available with combination therapy.

High blood pressure should be controlled to < 130/80 and should include some form of angiotensin II blockade as part of the program (ACE inhibitor or ARB). Both classes of agents decrease CV events, slow progression of renal disease and decrease development of T2DM.[13] (In DREAM, ramipril did not reduce the likelihood of progression to T2DM.) If one class is not tolerated, the other should be substituted. ACE inhibitors have been considered first choice because of decreased cost but do have more side effects (7% incidence of cough). However, a very recent network meta-analysis that included data from 143,153 patients in 22 clinical trials found that ARBs had less of an association with new-onset T2DM than ACE inhibitors, which came in second in an indirect comparison.[14] The debate will continue until these two classes are compared directly in a large head-to head study.

Other drug classes shown to reduce CVD in patients with T2DM (β-blockers, thiazides, and calcium channel blockers) should be added as needed to achieve the goal BP of < 130/80.[15]

Management of multiple risk factors calls for multiple therapeutic interventions. Whether or not to use combination therapy is no longer the question; rather, physicians should now be asking which combination is best? Drug therapies should be based on global risk assessment and should follow current treatment guidelines for each of the risk factors. MetS should serve to bring the cardiovascular and diabetes fields together in a joint effort to reduce both CVD and diabetes. With prevalence expected to double by 2050, diabetes prevention is an "urgent national priority".[16]

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