The prevalence of obesity in US adults increased by nearly 50% during the 1980s and 1990s, resulting in nearly 70% of adults being classified as overweight or obese vs. fewer than 25% four decades ago. Compared with overweight and mild obesity, the proportion with morbid obesity has increased by an even greater extent. The morbidity attributable to obesity is even greater vs. smoking, alcoholism, and poverty. Based on current projections, obesity may soon become the leading cause of preventable death in the United States (currently cigarette abuse).

**Study Highlights:** Overweight is defined as a Body Mass Index (BMI) of 25 to 29.9 kg/m² and obesity as BMI of 30 kg/m² or more. Indices of obesity that may have more predictive power vs. BMI include body fatness, waist circumference, waist-to-hip ratio, and weight-to-height ratio. In both adults and children, obesity has reached global epidemic proportions, which may result in an end to the steady increase in life expectancy. Many co-morbid conditions have been linked to obesity, including hypertension, type 2 diabetes (T2DM), and dyslipidaemia. In addition to T2DM, obesity may contribute to other increases in insulin resistance such as glucose intolerance and metabolic syndrome. Dyslipidaemia linked with obesity includes elevated total cholesterol; triglycerides; LDL-C; non-HDL-C; apolipoprotein-B; and small, dense LDL-C particles; and decreased HDL-C and apolipoprotein A-1 levels.

Obesity increases the risk for CV abnormalities, including LV concentric hypertrophy, endothelial dysfunction, increased systemic inflammation and a prothrombotic state, and systolic and diastolic dysfunction.

Obesity is linked to increased prevalence of CVD including heart failure, CHD, sudden cardiac death, and atrial fibrillation.

Non-CVD associated with obesity include obstructive sleep apnoea, sleep-disordered breathing, albuminuria, osteoarthritis, and specific cancers. The importance of obesity in the pathogenesis of CVD is confirmed by overwhelming evidence. Overall survival is decreased in obese patients.

The **obesity paradox** refers to the unexpectedly better short- and long-term prognosis, confirmed by evidence from clinical cohorts of patients with established CVD (hypertension, heart failure, CHD, and PAD) of overweight and obese vs. non-overweight/non-obese people with these diseases. *Reasons for the obesity paradox are unclear.*

Obese patients with hypertension may have a better prognosis vs. lean, possibly because of lower systemic vascular resistance and plasma renin activity. Excess body weight may offer some protection against heart failure mortality, perhaps because of more metabolic reserve and protective cytokines and neuroendocrine profiles.

Despite the obesity paradox, the bulk of evidence still supports voluntary weight loss for prevention and treatment of CVD. Lifestyle interventions (exercise and mild weight loss) may reduce risk for T2DM by nearly 60%.

Patients with hypertension who lose weight have significant decreases in arterial pressure. In heart failure, weight loss may be associated with improvements in left ventricular mass and in systolic and diastolic ventricular function.

Bariatric surgery is associated with short- and long-term reductions in major morbidity and all-cause mortality, particularly related to cancer, diabetes, CVD, and long-term lowering of CV risk.

**Clinical Implications:** Many co-morbid conditions are linked to obesity, including CV risk factors such as hypertension, T2DM, and dyslipidaemia. CV abnormalities associated with obesity include LV concentric hypertrophy, endothelial dysfunction, increased systemic inflammation and prothrombotic state, and systolic and diastolic dysfunction.

Despite the obesity paradox, the bulk of evidence still supports voluntary weight loss for prevention and treatment of cardiovascular diseases.

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Early signs of vascular disease in untreated type 2 diabetes

This cross-sectional study was undertaken to compare arterial stiffness among patients with newly-diagnosed, untreated type 2 diabetes (T2DM) or impaired glucose tolerance (IGT) with that in age- and sex-matched normoglycaemic individuals in a Malay population, in order to identify early manifestations of macrovascular diseases.

Commentary
It is well known from epidemiological studies that, compared with non-diabetic individuals, those with T2DM have an increased risk of macrovascular complications. The excess is not completely explained by the cluster of risk factors, such as hypertension, dyslipidaemia, and obesity that are associated with the disease. In the last decade, it has also been documented that micro- and macroalbuminuria confer reduced survival due to increased cardiovascular (CV) risk [1] This association is probably due to systemic atherosclerosis and reduced renal function acting as a marker, rather than a determinant of vascular dysfunction. Studies have also shown that in patients with diabetes, measurement of plasma apolipoprotein apoB and apoA1 improves the prediction of CV disease, allowing identification of high-risk individuals who are not identified by the standard lipid profile [2].

As there is one molecule of apoB per atherogenic particle, plasma apoB levels provide a measure of total number of atherogenic particles. The Steno-2 studies have pointed out that a reduction in CV risk in diabetes is feasible when all abnormalities are addressed together. In at-risk patients with T2DM, intensive intervention with multiple drugs and behaviour modification had sustained beneficial effects with respect to vascular complications and on mortality rates from any cause and from CV causes [3].

CV risk is increased even before the diagnosis of diabetes. Rahman et al. employed a case-control study design to compare people with newly-diagnosed diabetes, IGT, and normal GT, none of whom had any other CV risk factors. In spite of this favourable risk profile, people with diabetes had early manifestation of macrovascular disease, evidenced by increased arterial stiffness, measured by simple, non-invasive means over most major arterial segments.

Thus, in routine clinical practice, people at risk of diabetes should be screened and all risk factors treated simultaneously in order to prevent CV consequences of the disease [4].

Summary: Patients with T2DM have an increased risk of macrovascular complications compared with the general population. Arterial stiffness is considered to be an independent predictor of macrovascular events. This study investigated arterial stiffness in patients without any traditional CVD risk factors and with newly-diagnosed T2DM or IGT. After preliminary screening of 1,620 individuals, 30 T2DM patients and 30 with IGT were recruited and compared with 30 age- and sex-matched normoglycaemic individuals. The T2DM patients were newly-diagnosed, never-treated, normotensive, non-obese, non-hyperlipidaemic, and non-smokers. Haemodynamic variables, pulse wave velocity (PWV), and augmentation index (AI) were measured. The PWV was significantly higher in the patients with T2DM (10.37 ± 2.64 m/s vs. 8.70 ± 1.29 m/s; p = 0.035) and was of borderline significance in patients with IGT (9.54 ± 1.56 m/s vs. 8.70±1.29 m/s, p = 0.078) compared with normoglycaemic individuals. The AI was higher and of borderline significance in T2DM patients (134.53 ± 17.32 % vs. 129.17 ± 11.18 %, p = 0.055) and patients with IGT (132.02 ± 16.11 % vs. 129.17 ± 11.18 %, p = 0.059) compared with normoglycaemic individuals.

The authors concluded that newly-diagnosed, never-treated T2DM patients without any CV complications had early manifestations of macrovascular disease as evidenced by increased arterial stiffness. The findings also revealed early manifestations of preclinical vasculopathy and a potentially increased risk for development of macrovascular diseases at an early age in patients with T2DM.

References
Although LADA may appear to initially respond to similar treatment as type 2 diabetes, it will not halt or slow the progression of beta cell destruction.

LADA is neither classified as type 2 diabetes or type 1 diabetes but considered somewhere in between. It is a form of type 1 diabetes that has similarities and differences to both type 1 and type 2 diabetes. In general:

♦ **Onset:** Type 1 diabetes onsets more rapidly and at a younger age than does LADA. Onset of both LADA and type 2 diabetes is slow, over many months or years.

♦ **Family history:** There is often an absence of family history of type 2 diabetes in a LADA patient's family, but a genetic marker of HLA genes is found in type 1 and LADA, but not in type 2 diabetes. LADA does not affect children and is uncommon in young adults (age 25–30). It is most often diagnosed after age 35.

♦ **Antibodies:** Persons with type 1 diabetes and LADA usually test positive for certain (same) antibodies that are not present in type 2 diabetes.

♦ **GAD antibodies:** Persons with LADA usually test positive for GAD antibodies, whereas in type 1 diabetes these antibodies are more commonly seen in adults rather than in children.

♦ **Insulin sensitivity:** Persons with LADA are not insulin resistant (and may be insulin sensitive) as in the case of type 2 diabetes.

♦ **Lifestyle and excess weight:** Type 2 diabetes may onset as a result of a sedentary lifestyle and excess body weight (especially when excess weight is carried about the centre, or in those with an "apple" shaped body). These factors are not thought of as contributing factors to the onset of type 1 diabetes or LADA. Persons with LADA are often normal body weight or thin and are not insulin resistant. Persons with type 2 diabetes are often insulin resistant and overweight.

♦ **Prognosis:** About 80 % of all persons initially diagnosed with type 2, who also have GAD antibodies, will become insulin dependent within six years. Those with both GAD and IA2 antibodies will become insulin dependent sooner. LADA occurs slowly, but progresses towards insulin dependency.

**Treatment:** Although LADA may appear to initially respond to similar treatment (lifestyle and medications) as type 2 diabetes, it will not halt or slow the progression of beta cell destruction. People with LADA will eventually become insulin dependent.

**Point / Counterpoint: Should Insulin Therapy Be Started Earlier in Patients With Type 2 Diabetes?**

**Point:** Early use of insulin improves beta-cell function. We should be using insulin earlier in type 2 diabetes. More than 40 % of people with type 2 diabetes are not at the haemoglobin A1c goal of less than 7 %. More than 50 % are not at an A1c goal of 6.5 % or less. The problem, I believe, is that it's taking far too long to start insulin in subjects who are failing treatment with oral agents or other anti-diabetes medications other than insulin.

We suffer from clinical inertia. In one study, almost 50 % of physicians agreed that they prefer to delay initiating insulin until they consider it to be absolutely essential. The reality is that most patients with type 2 diabetes will fail to obtain their A1c goals with a conventional treatment paradigm. The typical approach to treat type 2 diabetes is diet and exercise, waiting for that to fail before using one drug, then seeing failure occur again before increasing the dose of that one medication, and finally deciding to introduce combination oral anti-diabetes medications. Years on other diabetes therapies pass before initiating insulin therapy.

Some studies show clearly that early use of insulin therapy restores and improves beta-cell function and can actually lead to remission of the disease. In one study, 16 patients with newly diagnosed type 2 diabetes were intensively treated with insulin for 2-3 weeks to achieve near-normoglycaemia. Insulin therapy was then stopped. After one year, normoglycaemia was maintained with diet in 7 of the 16 patients and with oral agents in 8 patients, and only 1 person needed insulin (Diabetes Care 2004;27:1028-32).

Another study took 138 patients with newly diagnosed type 2 diabetes and a mean fasting glucose of 240 mg/dl (13.3 mmol/l) and treated them with continuous infusion of insulin for two weeks. Normoglycaemia was achieved in 126 patients. (Continued on P.4)
They were followed on diet therapy alone for two years, during which 72 % were in so-called remission with near-normoglycaemia 3 months after stopping insulin (Diabetes Care 2004;27:2597-602).

I think there is evidence from these small clinical trials demonstrating the value of intensive insulin therapy and the impact that it has on beta-cell function. Let’s start insulin earlier in the natural history of the disease so that we can get more patients to A_1C goal and maintain that goal. Let’s employ an intensification approach to treating type 2 diabetes with a more aggressive treatment regimen based on earlier initiation of pharmacologic therapy, earlier up-titration of oral medication if appropriate, and earlier use of insulin to achieve and maintain glucose levels and haemoglobin A_1C levels at the targets that have been set in guidelines.

If we don’t use insulin at the time of diagnosis to achieve normoglycaemia, we at least need to use insulin earlier in the natural history of the disease to maintain good glycaemic control and reach therapeutic goals.

Dr. Abrahamson of Harvard Medical School, Boston, is medical director of Joslin Diabetes Center, Boston. He is a speaker for multiple companies that market insulin, and received research support from one of them, Pfizer Inc.

**Counter-Point:** Aggressive combination treatment is often enough.

Is there a compelling reason to add insulin early? Dr. Abrahamson cited a few studies that used intensive insulin therapy for a period of time, with some follow-up. Maybe there is something to that. But is it the insulin or aggressive early therapy in general that gets terrifically tight glycaemic control?

With more aggressive combination treatment using oral agents and insulin, the data rivals what Dr. Abrahamson presented for intensive insulin therapy. Aggressive combination therapy gets patients to an A_1C of less than 7 % more than 60 % of the time.

A recent study offered quite reassuring data showing improvement in A_1C levels in three sets of U.S. National Health and Nutrition Examination Survey data from 1999 through 2004. Each group shows improvement—patients who use pills only, insulin only, pills plus insulin, or diet only (Diabetes Care 2008; 31:81-6). If you look at the frequency of use, over this time frame, the percentage of people on these different treatments hasn’t really changed much. With each treatment, the proportion of patients with an A_1C less than 7 % increased in each of the groups. It argues against using insulin only, because pills are working as well, and treatment with pills plus insulin looks very similar in effectiveness.

It comes back to individualising therapy. It’s difficult to predict response in an individual patient. You have to try things.

There is patient resistance to insulin. Patients are knowledgeable about insulin; they’re afraid of what it means, and they know about some of the side effects. Patients think that this is the end of the line. You have to emphasise to them that we’re using insulin to get aggressive control.

Physician barriers also are quite significant. Most diabetes, especially type 2, is managed in primary care settings where there are no educators and nurses and people to teach the patient about the dosing of insulin. Many practising physicians lack the expertise to do this.

What about using combination therapy initially to treat diabetes? In one study, the A_1C level fell from 8.9 % to less than 7 % in 77 % of patients. That’s similar to the data reported when using insulin aggressively. We now have combination pills available that can be less expensive and have been proved to improve compliance.

Evidence is lacking that insulin offers a unique therapeutic benefit. In studies that suggest this, insulin wasn’t tested against another modality. There are potential barriers to insulin therapy among patients and the health care team. If you look at some of the emerging clinical trial data, early or initial oral combinations can be very effective. But I would not hesitate to add insulin to oral treatments when patients are not reaching their targets.

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