Only 40% Americans with type 2 diabetes (T2DM) and cardiovascular disease (CVD) - and just 20% in European countries – meet current BP goals, Benjamin A. Steinberg reported at the ESC/WHF meeting.

These findings from a huge contemporary international database underscore the urgent need for physicians to do much better at identifying and controlling high blood pressure in this very-high-risk population, Steinberg stressed.

During a year-long fellowship to conduct cardiovascular research, Steinberg, a medical student at Johns Hopkins University, analysed the CardioMonitor database for 1998-2004. CardioMonitor is an annual survey of outpatients with cardiovascular disease in multiple countries. It relies on medical records provided by primary care physicians and cardiologists.

For the years 1998-2004 excluding 2002, when the survey was not conducted, the CardioMonitor database included nearly 155,000 patients with CVD in the USA and five European nations. A total of 23,139 of these patients also had T2DM.

The prevalence of diabetes among cardiovascular patients rose during the years of the study, in some countries quite markedly. For example, the reported prevalence of T2DM among patients with CVD doubled in France and the UK between 1998 and 2004, while in the USA, it climbed from 15.1% to 20.5%. The prevalence in 2004 was greatest in Germany, at 24.9%. In Spain it was 19.5%, up from 11.8% in 1998, while in Italy the prevalence of T2DM among cardiovascular patients was just 9.6% in 2004.

The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure VII (JNC-VII) goal of a systolic blood pressure below 130 mmHg was achieved by only 41% of American diabetic cardiovascular patients. European rates were far lower, Steinberg said.

The less stringent ESC blood pressure target in place in 2004 – a systolic pressure below 140 mm Hg – was met by 72% of American patients, 53% in the United Kingdom, 49% in Spain, 47% in France, 44% in Germany, and 33% in Italy.

One-year data from a large trial have shown that intensive lifestyle intervention (ILI) can produce significant weight loss and reduce CV risk factors among patients with T2DM, F. Xavier Pi-Sunyer reported at the ADA.

The Look AHEAD (Action for Health in Diabetes) study is an ongoing 16-centre randomised clinical trial designed to determine whether intensive lifestyle modification-including both decreased caloric intake and increased physical activity-can reduce the rates of both fatal and nonfatal myocardial infarctions and strokes in overweight volunteers with T2DM over a planned follow-up of 11.5 years, compared with traditional medical care.

The study includes 5,145 patients with T2DM with a mean age of 59 and mean BMI of 36 kg/m2. 37% are from ethnic / racial minority groups. Approximately 15% are insulin users, and the same proportion have a history of a prior CVD event. They receive care from their own physicians in the community, while the study sites provide the intervention.
The ILI, to which 2,570 patients were randomised, consisted of an initial 6-month phase in which they attended three group sessions and one individual session per month, all conducted by trained diabetes educators and emphasising nutrition and physical activity aiming at a personal weight loss goal of 10% from baseline.

During months 7 through 12, subjects attended two or three sessions per month, either individually or in a group. Those who had achieved the first goal were aiming to maintain their weights, while those who had not continued to aim for the 10% loss.

Calorie recommendations were calculated based on baseline and goal weights, initially set at 1,200-1,500 kcal/day for those weighing 250 pounds or less at baseline and 1,500-1,800 kcal/day for those weighing more than 250 pounds. Participants could choose a regimen that included liquid meal replacements. Exercise was gradually increased to at least 25 minutes/day. Most participants walked, aiming for 10,000 daily steps, said Pi-Sunyer, professor of medicine at Columbia University.

The 2,575 control patients received diabetes support and education (DSE) consisting of three to four group meetings per year in which diet, exercise, and social support were discussed but no intervention was actually delivered.

Of the 97% of study subjects who attended the 1-year exam, the ILI group had lost a mean of 8.3% of their body weight, compared with 0.4% in the controls, a highly significant difference. The average weight loss was about 18 pounds. The ILI group continued to lose weight for about the first 8 months of the study, after which their weight tended to plateau but did not rebound.

On average, the men lost about 3-4 pounds more than the women did. By race, whites lost a mean of 10% of their baseline body weight, compared with about 6.5% for Hispanics and African-Americans and 6% among Native Americans. The 385 insulin users in the group lost a mean of 7% of their baseline body weight, and the 1,464 on oral anti-diabetes medications lost 8%, while the 326 not taking any medications lost the most, with a mean of 9%.

Fitness, as measured by treadmill testing, improved by 16% in the ILI group and 11% in the controls, after adjustment for weight loss. Fitness improved significantly across all BMI's and in both genders and all the ethnic/minority groups. Changes in fitness were highly correlated with changes in activity level and in body weight.

Haemoglobin A1c levels dropped from 7.25% at baseline to 6.6% at 1 year in the ILI group, a highly significant difference. In contrast, the drop from 7.3% to 7.15% in the DSE group was not significant. Similarly, fasting glucose dropped by a mean of 21.5 mg/dL with ILI, compared with just 7.2 mg/dL in the DSE group. The improved haemoglobin A1c occurred despite a greater reduction in glucose-lowering medications in the ILI group.

Systolic blood pressure dropped by 6.8 mm Hg in the ILI group vs. 2.8 mm Hg with DSE, and diastolic by 3.0 mm Hg vs. 1.8 mm Hg. Again, the reduction was significant only for ILI. While LDL cholesterol levels did not change significantly in either group, HDL cholesterol rose to a greater degree with ILI (3.4 vs. 1.4 mg/dL). Triglycerides dropped by 30.3 mg/dL with ILI, compared with just 14.6 mg/dL for DSE.

At 1 year, the ILI group was taking an average of 2.7 medications for glucose, blood pressure, and/or lipid lowering, compared with 3.2 for the DSE group. Continued intervention and follow-up will determine whether these changes will be maintained and lead to a reduction in cardiovascular events.

**Does an adolescent’s type 2 diabetes work like an adult’s?**

**Summary:** A US study showed that the primary metabolic defects that characterise type 2 diabetes in adolescents are similar to those previously observed in adults: increased insulin resistance and impaired insulin secretion in relation to the degree of insulin resistance.

**Commentary**

Type 2 diabetes in adolescence is an emerging problem. Of American cases of diabetes, 10-45% are thought to be type 2, whereas in Europe the prevalence of T2DM is still low. It is likely that the disease is also on the increase in Europe. As such, precise prevalence is difficult to estimate. T2DM is still a clinical diagnosis leading to a self-fulfilling prophecy that such patients are obese, not insulin dependent (in most cases), and older at onset than patients with T1DM.

There is no doubt that the epidemic of obesity is the major cause of the increase in T2DM, and possibly even the increase in T1DM. Obesity leads to a relative increase in insulin resistance and a decreased insulin sensitivity, both of which lead to an increased requirement for insulin.
In searching for preventative measures and optimal treatment, the metabolic defects behind the disease are highly relevant. This study confirms that diabetes in adolescence is similar to diabetes in adults. It also confirms that the obese adolescents with diabetes have increased blood sugar levels during an OGTT when compared with both the lean and non-diabetic obese adolescents; the obese non-diabetics had the same glucose levels as their lean counterparts. Increased C-peptide and insulin levels form part of the definition of T2DM upon which the study is based, so the increased FPG in the diabetic subjects come as no surprise. What is far more interesting is that the insulin response to the OGTT is the same in the obese and the diabetic adolescents. This means the insulin secretion capacity is the same, but it is impaired relative to their degree of insulin resistance.

Unfortunately, the diabetic subjects are more obese (BMI = 36.8) than the non-diabetic obese group (BMI = 33.5), leaving the question of whether insulin secretion would have been less if compared to a group without diabetes but with the same level of obesity. Insulin production may have been higher prior to the development of diabetes, or they may have reached a maximum and therefore developed diabetes. The BMIs reported for the patients with diabetes were recorded at diagnosis, perhaps differing from the actual BMI at the time of testing.

Another problem is the differences in ethnicity, as there are known differences between different ethnic groups with regard to insulin resistance and sensitivity. There are very few black people in the lean group but the obese and diabetic groups are more heterogeneous.

The unanswered question concerns whether there is a "point of no return" when it comes to diabetes and obesity. Is there a point where weight loss is ineffective at preventing diabetes and ineffective at improving the glucose metabolism in a patient because the damage to β-cells has been too high? We know that apoptosis of β-cells is accelerated because the metabolically active β-cells are more vulnerable to cytokine damage. We know that physical activity and weight loss prevents diabetes, or does it just postpone the disease? Another question is whether it is the duration of obesity or the level of obesity that is the most important factor. For adolescents with T2DM, the indications are that for some it is the level of obesity.


Summary
The prevalence of T2DM in adolescents in the USA is increasing at an alarming rate in parallel with the growing epidemic of childhood obesity. The primary metabolic defects that characterise type 2 diabetes in adults have been researched extensively and are known to be a combination of insulin resistance and impaired insulin secretion from the β-cells in the pancreas. In contrast, the metabolic defects that characterise T2DM in adolescents are less well known. Therefore, the aim of this study was to determine the major factors that contribute to T2DM in this younger age group.

USA Researchers studied insulin sensitivity and pancreatic islet-cell function in 16 adolescents with T2DM and compared the results with 13 obese and 13 lean adolescents without diabetes. Blood samples were taken following an overnight fast and after glucose was administered.

Adolescents with T2DM had significantly higher mean fasting glucose and insulin levels compared with obese and lean controls. The diabetic adolescents were shown to be 3- to 4-fold more insulin-resistant than the obese and lean controls (p < 0.05). In addition, the β-cells of the adolescents with diabetes were unable to compensate for the insulin resistance. Whilst the diabetic adolescents secreted an amount of insulin in response to glucose that was comparable to the lean controls, this response was shown to be insufficient for their degree of insulin resistance (assessed by adjusting insulin secretion for insulin resistance).

The ability of the β-cells to process proinsulin to insulin was also determined and was shown to be comparable amongst the three groups, both in the fasting state and after glucose was administered. In addition, plasma glucagon was similar in the three groups after an overnight fast and after glucose ingestion, implying that there was still an α-cell response to elevated glucose in the diabetic adolescents.

The authors concluded that the primary metabolic defects that underlie type 2 diabetes are similar in adolescents and adults. However, the adolescents with type 2 diabetes in this study did not demonstrate the abnormalities in insulin processing and altered glucagon responses to raised glucose levels that are commonly found in adults with this disease.

Rosiglitazone Reduces Risk of Progression from Pre-diabetes to Type 2 Diabetes by 62% in Largest-ever Diabetes Prevention Trial

In the largest diabetes prevention trial ever conducted, rosiglitazone (Avandia®) reduced the risk of developing T2DM by 62% relative to placebo among people at high risk of developing T2DM. This highly significant reduction of 62% (p<0.0001) was additive to standard counselling on healthy eating and exercise.

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial evaluated the likelihood of progression to T2DM over a 3-year median follow-up period among 5269 with ‘pre-diabetes.’ Patients in the study were randomised to rosiglitazone (8 mg daily) or placebo and to ramipril (15 mg daily) or placebo and were assessed every 6 months for 3-5 years to determine if rosiglitazone or ramipril can reduce the risk of developing T2DM in pre-diabetic patients, when added to healthy eating and exercise counselling. The DREAM study was not designed as a direct comparison between rosiglitazone and ramipril.

In this study, designed and conducted at McMaster University, 10.6% of people receiving rosiglitazone progressed to T2DM versus 25% of people treated with placebo. In the composite primary endpoint of development of diabetes or death from any cause, rosiglitazone demonstrated a 60% risk reduction relative to placebo (p<0.0001).

"The DREAM findings are particularly significant as we are in the midst of an epidemic of T2DM with global implications. It is also noteworthy that the damaging complications of T2DM can often precede the diagnosis of this condition by several years," said Bernard Zinman, DREAM Steering Committee Member. "By demonstrating that rosiglitazone significantly reduced the risk of developing T2DM, these data provide important evidence that it may be possible to alter the course of rising blood sugar levels and its consequences."

Over the three-year median follow-up period of the trial, 51% of the people receiving rosiglitazone returned to normal blood sugar levels compared to 30% of people receiving placebo; thus, people taking rosiglitazone were about 70% (p<0.0001) more likely than those taking placebo to return to normal blood sugar levels. As might be expected, people in the placebo group with higher BMI, an indicator of obesity, were more likely than those with lower BMI to progress to diabetes. However, the risk of developing diabetes did not increase with BMI in the group randomised to rosiglitazone. These findings suggest that rosiglitazone may reduce the increased risk of developing diabetes that is attributable to obesity.

We believe the long awaited findings from the DREAM trial will lead to a better understanding of T2DM and its treatment," said Lawson Macartney, senior vice president, GSK. "The DREAM trial is the largest diabetes prevention trial conducted to date and provides the first body of evidence that rosiglitazone can reduce the risk of progression from pre-diabetes to T2DM in high-risk patients."

Rosiglitazone belongs to the thiazolidinedione class of drugs and is an approved treatment for type 2 diabetes. No agent (including rosiglitazone) is currently approved for the treatment of pre-diabetes.