Glucose Metabolism Changes Evident 13 Years Before Diabetes

The British prospective Whitehall II study shows “...changes in glucose, insulin sensitivity, and insulin secretion as much as 3 to 6 years before diagnosis of diabetes.” Insulin resistance and beta-cell dysfunction are evident up to 13 years before diagnosis, but the changes really begin to accelerate in the 3 to 4 years before diagnosis.

These results were presented at the ADA in New Orleans by Adam Tabak. Whitehall II involved 6538 subjects without diabetes at baseline. Nearly all (91%) were white and 71% were men. Age range at baseline was 35 to 55 years.

The investigators measured fasting and 2-hour post-load glucose levels, insulin sensitivity, and beta-cell function for an average of 9.7 years, but for as long as 13 years before a diagnosis of diabetes was made. During follow-up, 505 diabetes cases were diagnosed, with 49.1% of diagnoses made on OGTT.

“All metabolic measures followed linear trends in the group of non-diabetics except for insulin secretion that did not change during follow-up,” Tabak et al report in their abstract. Among diabetics, fasting glucose was accompanied by “…a steep quadratic increase.” Fasting glucose levels averaged 5.79 mmol/L at baseline and increased to 7.40 mmol/L “…starting three years before a diagnosis of diabetes,” Tabak et al report.

Two-hour post-load glucose “…showed a rapid increase starting three years before diagnosis,” from 7.60 mmol/L at baseline to 11.90 mmol/L after 3 years.

Steep Increase Before Diagnosis

Insulin resistance was evident 13 years before diagnosis. “There was a faster increase beginning at about four years. By the year before diagnosis, there was a very fast, very steep increase,” Tabak reported. Insulin sensitivity “decreased steeply during the 5 years before diagnosis, to 86.7%,” he said. "Beta-cell function showed a compensatory increase beginning 13 years before diagnosis. At 3-4 years before diagnosis, beta-cell function increased from 85.0% to 92.6% at the time of diagnosis. Beta-cell function decreased to 62.4% after the diagnosis of diabetes had been made.”

“The description of biomarker trajectories leading to diabetes diagnosis could contribute to more accurate risk prediction models that use repeated measures available for patients through regular check-ups,” the authors write.

“We think that our study confirms on a population level that both insulin resistance and beta-cell dysfunction are already present years before diagnosis,” Tabak stated. “We hope that this might help build new risk prediction models that make use of the wealth of repeated measures of glucose already present in patient records over the years in clinical practice during regular check-ups and point to window of opportunity of screening and prevention.”

Prevention More Effective in Preclinical Period

“It also supports hypothesis that prevention is more effective in the preclinical period, before the classic symptoms are evident,” Tabak said. His conclusion was echoed by R. Paul Robertson, the American Diabetes Association’s president of medicine and science, and an endocrinologist at Swedish Medical Centre in Seattle, Washington. “I recommend treating patients when they have prediabetes, when impaired glucose metabolism is present, but A1C levels might still be normal,” Robertson told Medscape Diabetes & Endocrinology. “Early, aggressive treatment might prevent some of the complications of diabetes that might already be present by the time the diagnosis is made.

“And early intervention might head off some cases of prediabetes from developing into overt diabetes,” he added. “Prediabetes does not mean that diabetes is inevitable.”

American Diabetes Association (ADA) 69th Scientific Sessions: Abstract 1050-P
Despite being a key cause of heart disease, obesity appears to be protective in a range of cardiovascular problems, a new review concludes [1]. But that doesn’t mean people shouldn’t try to lose weight, lead author on the paper, Carl J Lavie told heartwire. Indeed, patients who fare the best seem to be obese patients who manage to lose some weight.

"First, obesity is a very strong risk factor and increases all types of heart disease, but second, once you get heart disease, the obese patients do better, so their prognosis is not doomsday," Lavie explained. "In fact, if you have obese patients with congestive heart failure or coronary heart disease (CHD) or other heart disorders, those patients actually have a pretty good prognosis if they are treated well. But third, the ones who lose weight do even better." According to Lavie, there is solid evidence to suggest that being overweight or obese may improve survival, not just in heart failure, but also in diseases like hypertension, coronary artery disease (CAD), and peripheral artery disease (PAD).

"There are a large number of cardiologists who don’t even recognise that this is the case and they are confused about it, too. It is honestly a confusing topic because if obesity is so bad, and it contributes to all CV risk factors and markedly increases the prevalence of developing heart disease of almost every type, then why, once they get it, do obese patients do better?"

### Obesity Likely Protects Through Various Mechanisms

The protective effects of excess weight have been best documented in heart-failure patients, where patients with higher body weight or % body fat demonstrate better event-free survival. In this setting, says Lavie, extra weight may function much the same way it does with cancer and other chronic diseases, by providing the body with additional fuel to help fight the disease. Less well known is the relationship between obesity and hypertension, Lavie et al note. While people who are obese do have more hypertension, five papers spanning almost 20 years also point to the fact that obese people with hypertension seem to have lower mortality and / or lower stroke risk, despite less effective BP control, than do normal-weight people. In this setting, obese patients "may have a better prognosis in part because of having lower systemic vascular resistance and plasma renin activity compared with more lean hypertensive patients," Lavie et al write. Also incompletely understood is the paradoxical relationship of obesity and CAD and PAD. Obesity is believed to play a causal role in the development of a number of major risk factors for arterial disease, among them hypertension, dyslipidaemia, and diabetes, and is believed to be, in and of itself, a risk factor for atherosclerosis. But according to the authors, there is also literature to suggest that overweight and obese CHD patients have a lower risk for mortality compared with under- and normal-weight CHD patients who have undergone revascularisation procedures. A similar contradictory relationship has been seen in patients with PAD.

Speaking with heartwire, Lavie emphasised that the protective effects of excess weight and excess fat likely function in different ways in different diseases. "We know that fat cells do a lot of bad things, but it's certainly conceivable that in advanced disease, the fat cell could have some beneficial effects. There's still a lot that needs to be known about this process."

### Weight Loss Still Key

A key new piece of the puzzle that emerged in Lavie et al's review, however, is that weight loss, often touted as a way to reduce CV risk, appears to be a good thing in spite of the protective effects of extra weight. "For people who follow this field, these kinds of findings have led them to question whether weight loss is good for heart-disease patients. We found that the patients who do the best are the obese patients who lose weight."

This additional contradiction may be explained in part by the theory that heart disease in obese patients is likely "a different disease" than heart disease in lean people, in whom genetic factors are probably more important. "It may be that the obese person wouldn't have even got blocked arteries if [he] hadn't gained 70 pounds over a 30-year period," Lavie said. "The thin person who gets blocked arteries or congestive heart failure or high blood pressure is probably different from the obese patient who got the disease from becoming obese." For now, he says, it's important particularly for the general public to appreciate that the "protective" effects of obesity in no way provide a rationale for weight gain. "Very clearly," he said, "if no one in our country became overweight or obese, heart-disease rates would go down dramatically."

For physicians, the data today are sufficiently comprehensive for them to encourage their overweight and obese patients to stay motivated to reduce their risk factors. That wasn't always the case, he added. "When people were finding this in their data, five and six years ago, they probably had some trouble getting their papers published, because it didn't make any sense."

### Reference

Several short-term studies in insulin-treated type 2 Diabetes Mellitus (T2DM) patients have shown metformin can improve glycaemic control and reduce insulin requirements and weight gain," write Adriaan Kooy et al, from Netherlands. "To our knowledge, the long-term beneficial effects of metformin in such patients have not been studied. We hypothesised that, in patients with T2DM treated with insulin, metformin, compared with placebo, will have sustained beneficial metabolic effects, even at the same level of glycaemic control, and thus decrease (cardio-)vascular disease."

In the outpatient clinics of 3 hospitals, 390 patients treated with insulin were randomly assigned to receive metformin 850 mg, or placebo (1–3 times daily), added to insulin therapy. The main study outcome was an aggregate of microvascular and macrovascular morbidity and mortality during a follow-up period of 4.3 years. Secondary outcome measures were separate aggregate scores for microvascular and macrovascular morbidity and mortality, as well as effects on A1C, insulin requirement, lipid levels, blood pressure, body weight, and body mass index. Compared with the placebo group, the metformin group had prevention of weight gain (mean weight gain, −3.07 kg; range, −3.85 to −2.28 kg; \( P < .001 \)), better glycaemic control (mean reduction in A1C, 0.4%; 95% confidence interval [CI], 0.55–0.25; \( P < .001 \)), and lower insulin requirements (mean reduction, 19.63 U/day; 95% CI, 24.91–14.36 U/day; \( P < .001 \)).

Although metformin was not associated with an improvement in the main outcome, it was associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61; 95% CI, 0.40–0.94; \( P = .02 \)), which was partly explained by the difference in weight between groups. To prevent 1 macrovascular end point, the number needed to treat was 16.1 (95% CI, 9.2–66.6).

"Add-on metformin improved glycaemic control and reduced weight and insulin requirements," Nikolaos Papanas, at Democritus University in Greece, told Medscape Diabetes & Endocrinology when asked for independent comment. "Metformin did not improve the primary endpoint. However, it was associated with an almost 40% improvement in the secondary macrovascular endpoint." Papanas notes that this significant effect on macrovascular disease agrees with data from the UKPDS at 20-year follow-up, which showed a 33% reduction in myocardial infarction (N Engl J Med 2008;359:1577-1589).

"The strengths of the study are that it is the first randomised controlled trial on the effects of metformin specifically in insulin-treated patients," Papanas said. "A further strength is the relatively long follow-up period (4.3 years). Moreover, the authors achieved a sustained participation of patients in the trial."

Limitations of this study include its small sample size, and consequently limited power; the combination of separate microvascular and macrovascular clinical events; an imbalance between the 2 treatment groups after randomisation; a possible lack of generalizability to patients receiving less intensive care; and the performance of multiple analyses, suggesting that the positive finding on the secondary end point might possibly be a result of chance.

"A further limitation is the absence of a clearly documented mechanism by which the observed effects could be explained," Papanas said. "Indeed, long-term use of metformin contributes to the reduction of weight gain and to the improvement in metabolic control, while it may also have a very modest beneficial effect on blood pressure and serum lipids."

Because of contraindications to metformin use, metformin should be avoided in high-risk patients to avoid the danger of lactic acidosis (Acta Clin Belg. 2009;64:42–48). The authors of the present study conclude that their findings support the policy to continue metformin treatment after insulin is introduced in any patient with T2DM, unless contraindicated.

"Future research is needed into the long-term effect of metformin on cardiovascular morbidity in insulin-treated type 2 diabetic patients," Papanas concludes. "We also need to clarify the mechanisms of the beneficial action of metformin and identify to what extent this action is attributable to the reduction of body weight and insulin requirements, to the amelioration of insulin resistance and, possibly, to additional pleiotropic actions."

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A significant percentage of diabetes in children in all age groups is probably non-autoimmune in origin, with a remarkable increase after age 10 years, Jian Wang et al reported (J. Clin. Endocrinol. Metab. 2007;92:88-92).

This conclusion was drawn from a study in which 859 children with newly diagnosed diabetes were tested for four anti-islet autoantibodies: insulin autoantibodies (IAA), glutamic acid autoantibodies (GAA), islet cell autoantibodies (ICA), and islet cell autoantibody 512 autoantibodies (ICA512AA), and including two constructs of ICA512 (ICA512bdc and IA-2ic). Human leukocyte antigen genotypes, BMI, and HbA1c levels also were measured.

The study included 441 males and 418 females, ranging in age from 1 month to 18 years (mean 10.7 years). Of these, 685 were white, 55 Hispanic, 37 black, 35 other, and 47 unknown. Overall, 54% of cases were diagnosed between ages 9 and 14 years. With the three autoantibody assays of micro-IAA, GAA, and ICA512AA (ICA512bdc construct only), the positivity of autoantibodies was 79.4% (689 of 868). But by using the alternative ICA512 construct, IA-2ic, in 177 patients, followed by ICA testing in 167 patients, the investigators were able to identify 18 additional autoantibody-positive patients, yielding a final rate of 81.5% for autoantibody-positivity.

This finding meant that a surprising 159 of the 859 children (18.5%) were autoantibody negative. Previously, it was reported that about 4%-7% of patients with newly diagnosed type 1 diabetes are autoantibody negative, according to Wang et al, at the Barbara Davis Center for Childhood Diabetes, University of Colorado. Autoantibody negativity was equally distributed in both genders (80 of 441 males, 79 of 418 females).

Autoantibody positivity was 83% among children with diabetes onset under the age of 4 years, and the rate declined rapidly with age, reaching about 20% after age 15 years.

Autoantibody negativity varied significantly by ethnic group, although the number of Hispanic and black children in the study was limited. Autoantibody negativity was identified in 101 of 685 (15%) whites, 16 of 55 (29%) Hispanics, and 14 of 37 (38%) blacks. The difference between Hispanics and blacks in autoantibody negativity was not significant, and the difference among all three races was mostly in children > 14 years, the authors wrote.

Autoantibody negativity was significantly increased in children within three BMI cut-offs: 27.5% for BMI more than 1 standard deviation above the mean, 36.6% for BMI more than 1.5 standard deviations above the mean, and 43.4% for BMI > 2 standard deviations above the mean.

Hispanic and black children aged 10 and older with higher BMIs than those of white children had significantly increased autoantibody negativity. The data are consistent with previous observations that Hispanic and black children have a greater tendency to develop type 2 diabetes, the authors wrote.

There was no significant difference in HbA1c levels between the autoantibody-positive and autoantibody-negative patients, although HbA1c levels were positively correlated with age of diabetes onset in both groups.

“A reciprocal prevalence of autoantibodies associated with ages suggests a potential mechanism of differential islet autoimmune pathogenesis at different age groups,” the authors concluded.