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Prevention of Cardiovascular Complication in the Dysglycemic Stages IGT and Type 2 Diabetes with optimal antihyperglycemic Treatment

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The pandemic of prediabetes and type 2 diabetes in the last decades, and the recognition that IGT and Type 2 diabetes are major cardiovascular risk factors with an rapidly increasing contribution to morbidity and mortality have made effective treatment of hyperglycemia a top priority. Prospective studies have shown that all components of the gluco-triad: fasting hyperglycemia, postprandial glucose excursion and HbA_{1c} are closely related to cardiovascular events. Within the gluco-triad postprandial glucose excursions by multiple harmful effects on the vessel wall obviously are a risk factor in its own right. We now have evidence from controlled intervention studies in type 1 (DCCT), type 2 (UK-PDS, others) that a reduction of HbA_{1c} to ~ 7 % has beneficial effects on micro- and macrovascular complications. The Diabetes Intervention Study (DIS) in newly diagnosed type 2 diabetes and the STOP-NIDDM study in IGT resp. have shown that improved control of postprandial hyperglycemia is associated with lower incidence of cardiovascular events and (for DIS) with lower mortality. In the PROactive trial pioglitazone a PPARγ agonist improving insulin sensitivity significantly reduced incidence of cardiovascular events (secondary objective).

By extrapolation of prospective studies considering dysglycemia as cardiovascular risk factor it can be concluded that all components of the gluco-triad exhibit a continuous relationship to cardiovascular risk up to the normal range. The upper limit of normal for HbA1c is 6.1 % with the DCCT standard assay. For fasting plasma glucose the ORIGIN study set a target of 5.3 mmol/l and the upper limit of normal 2 hour postprandial/postchallenge plasma glucose is about 6-7 mmol/l. The target by the IDF for HbA_{1c} is < 6.5 % and by the ADA < 7 %. Recently in a consensus statement by the ADA and EASD it was proposed on the basis of practicability that the HbA_{1c} in the indivual patient should be as close to normal (< 6 %) as possible without significant hypoglycemia. This only can be achieved with a near to normal control of postprandial glucose excursion.

Lifestyle intervention studies have been successful only in preventing diabetes in people with IGT. Metformin in the DPP significantly reduced incidence of diabetes in IGT. The STOP-NIDDM examiniting successfully acarbose as a means of diabetes preventing showed in addition a significant decrease in myocardial infarction and 'any cardiovascular disease' (CVD).

Medications

Metformin reduces HbA_{1c} by 1-1.5 %. The UK-PDS has shown a beneficial effect on CVD outcomes. Sulfonylurea are equally effective, but increase weight, no significant effect on CVD proven, may be harmful. Glinides better control postprandial glucose with less risk of hypoglycemia, effect on CVD unknown. α-Glucosidase inhibitors reduce HbA_{1c} by 0.5-1 % with no weight gain and no risk of hypoglycemia. They specifically reduce postprandial glucose excursion. In the MERIA-metaanalysis a significant reduction in CVD was reported. Glitazones improve insulin sensitivity with a reduction of HbA_{1c} by 0.5-1.4 %. Their intake is associated with weight gain and edema. In the PROactive study a reduction of CVD was observed by pioglitazone compared to placebo. An increase in heart failure has been reported but not for fatal heart failure.

Insulin is the most effective and oldest medication. It bears the risk of hypoglycemia and weight gain. Insulin improves endothelial function and prevents microvessel disease. No prospective controlled study has reported significant effects on CVD so far. Better results may be obtained with early use of insulin.

For perfect control of the gluco-triad early combinations of metformin with acarbose, glitazones or glinides based on pathophysiology and individual needs frequently result in an near to normal control of hyperglycemia. The benefit of combinations for CVD out comes need to be confirmed.