

Expert Views in Diabetes

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Professor Hertzel C Gerstein is Professor in the Department of Medicine and the Department of Clinical Epidemiology and Biostatistics, and Director of the Division of Endocrinology and Metabolism at McMaster University, Hamilton, Ontario, Canada. He is also Director of Diabetes

Hamilton, Director of the Diabetes Care and Research Program (Hamilton Health Sciences [HHS]), Head of Endocrinology Service (HHS) and

Consultant in Endocrinology and Metabolism for HHS. Professor Gerstein is the first Chair holder of the Population Health Institute Chair in Diabetes Research, sponsored by Aventis Pharma Inc, at McMaster University. His research focuses on clinical trials and epidemiologic studies related to the prevention and therapy of diabetes and its consequences. Professor Gerstein achieved his MD at the University Of Toronto Faculty Of Medicine and attained his MSc in Design, Measurement and Evaluation from McMaster University Faculty of Health Sciences, in 1989. He is the recipient of a number of academic awards and was inducted into the McMaster University Alumni Gallery in 2002.

Insulin therapy in type 2 diabetes: can it offer both cardiovascular protection and β -cell preservation?

An edited transcription of a presentation given by Professor Hertzel C Gerstein during the Steno Diabetes Update Symposium on 26–27 January 2006 at the Hotel Marienlyst, Helsingør, Denmark

Insulin therapy in type 2 diabetes is an area that is evolving considerably. Not long ago, insulin had the aura of being the last possibility of therapy; the thing to use when everything else fails, and that persists today. I hope to show you that this is not necessarily true and that, in fact, the exact opposite may be true.

Is glucose level a risk factor for CV disease in people with diabetes or dysglycaemia?

Glycated haemoglobin, or HbA_{1c}, is a good measure of integrated glycaemia. In a meta-analysis of data from people with diabetes, HbA_{1c} was measured at baseline and patients were followed into the future.¹ All of the estimates were controlled for age, and some were controlled for sex, blood pressure, and a variety of

other factors. The pooled analysis showed that a 1% higher HbA_{1c} predicts an 18% higher risk of cardiovascular (CV) disease.¹ Thus, there is a progressive relationship between HbA_{1c} and CV risk in people with diabetes.

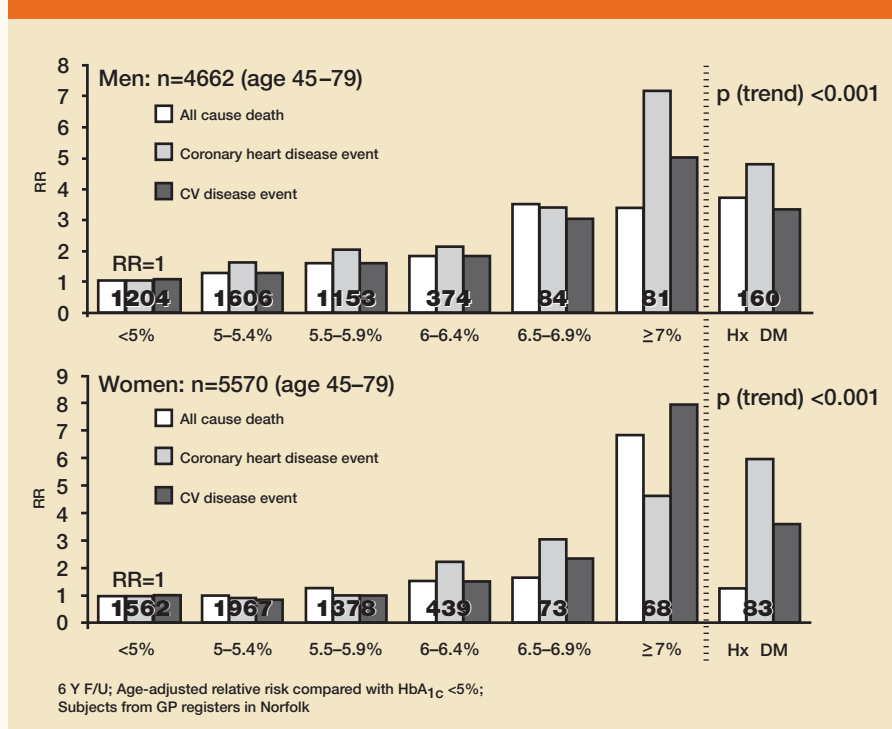
Does a similar relationship exist in people without diabetes? In a 6-year follow-up of 4,662 men and 5,570 women, CV events were measured according to A_{1c} groupings at baseline (Figure 1).² The vast majority of people had A_{1c} levels <6.4%, and very few had a history of diabetes. In this cohort study, the risk of all cause death, coronary heart disease (CHD) events and CV disease (CVD) events rose with the HbA_{1c}, with no clear lower threshold according to a curvilinear relationship (that is, qualitatively

similar to the relationship between other established CV risk factors and CVD). When the data are adjusted for age and diabetes, a 1% rise in HbA_{1c} predicts an approximately 30% increase in the risk for CVD events, CHD events or death in women, and a 25% increase in men. The fact that the relationship persists after adjustment for diabetes² strongly suggests that it is the degree of glycaemia and not the presence or absence of diabetes *per se* that is the driving factor.

Is there a link between glucose and CV risk?

One of the best analyses of the relationship between fasting glucose levels and CV risk was published in 2004 in *Diabetes Care*. This single-participant meta-analysis of data

Figure 1. A_{1c} and risk of cardiovascular events²



from the Asia-Pacific Cohort Studies Collaboration involved 237,468 individuals aged ≥ 20 and comprised 1.2 million person years of follow-up. It showed that for every 1 mmol/L higher fasting glucose level (above 4.9 mmol/L), there is a 21% higher risk of stroke, a 23% higher risk of total ischaemic heart disease, and a 19% higher risk of CV death, after taking sex, study and age into account.³ Moreover, the relationship was not affected by diabetes status; indeed, most of the people did not have diabetes. This analysis therefore clearly demonstrates the relationship between fasting glucose levels and subsequent risk for CV events.

Other meta-analyses, including the DECODE analysis, show a strong relationship between post-load glucose levels and CV events. Moreover, these analyses showed that if both fasting and 2-hour glucose levels are in the same equation, the 2-hour glucose level accounts for all of the glucose-related risk.⁴ In light of analyses such as these, it is typically concluded that the 2-hour glucose levels are the real predictor of CV

events and are much more important than the fasting glucose level. In one respect, that is true, as it is likely that the 2-hour glucose level contains all the information that is contained in the fasting glucose level, in addition to even more information. But I think that the question of whether the fasting or post-load glucose is more important is the wrong question. To borrow an example from cardiology, a resting ECG may certainly reveal something about that person's future CV risk, but an exercise ECG will reveal much more. If one therefore views the postprandial glucose level as the results of a metabolic stress test, it is clear that it imparts more information than the 'resting' glucose level, but clearly, if this measurement is not available, the fasting glucose provides important information.

So, this brings us to the concept of dysglycaemia. If one contemplates the metabolic status of the population, the people with diabetes (i.e. those with glucose levels above the diabetes threshold) are at high risk of eye,

nerve and kidney disease; they are also at high risk of CV disease, dementia, cognitive dysfunction, erectile dysfunction, neurological complaints, polycystic ovary syndrome and other diseases. The people whose glucose levels are below the diabetes threshold are at low risk for kidney, eye and nerve disease; however, they continue to be at high risk for CV and possibly the other conditions mentioned before. This continuum of glucometabolic abnormalities or dysglycaemia in the population therefore represents a continuum of risk for CVD (and possibly other health problems), and the diabetes threshold is just a 'waystation' that demarcates the addition of microvascular problems to this list.

Why is there a link between glucose and CV risk?

There are several possible reasons for a link between glucose and CV disease. An elevated glucose level may be toxic to blood vessels or to the heart itself; a reduced effect of insulin may increase vascular damage; insulin resistance and hyperinsulinaemia may promote vascular damage; or some proximal genetic or environmental risk factor may increase the risk of both dysglycaemia and CV disease.

So let us explore these possibilities a little bit. What about the effect of an elevated glucose level *per se*; what does high glucose do? When glucose is high, glycation occurs; this certainly includes glycation of haemoglobin, but also of blood vessels, collagens, lipids and red blood cells; glycated low-density lipoprotein (LDL), for instance, is more atherogenic than non-glycated LDL. Elevated glucose levels may also promote secretion of stress hormones, leading to increased blood pressure, renin-angiotensin system activation, increased PAI-1 levels and an increased level of inflammatory and procoagulant markers.

An excellent paper by Michael Brownlee in *Nature* in 2001 gives some insight into cellular pathophysiology mechanisms in response to excess glucose levels.⁵ As you know, as glucose enters a cell it is phosphorylated and enters the glycolytic pathway. At various points along the road to the mitochondria, it may activate various pathways (Figure 2). These include the polyol pathway, which produces sugar alcohols and reduces cytoplasmic antioxidants such as glutathione. If fructose-6-P accumulates, it activates the hexosamine pathway leading to inflammatory processes and coagulation gene activity. If glyceraldehyde-3-P accumulates, it can activate the Protein Kinase C pathway, which can reduce nitric oxide synthase and fibrinolysis, and increase endothelin, vascular permeability and inflammatory gene activity. This activates the advanced glycation endproduct (AGE) pathway, increases accumulation of AGE-related glycosylation end-products, and has potential cardiotoxic effects. In addition, high levels of pyruvate, which enter the mitochondria, promote production of superoxides, which themselves can damage DNA and the cells' ability to reproduce.⁵ These processes

may affect vascular cells as well as the β -cell.

Could the consequences of a high glucose level be due to a reduced effect of insulin, or the compensatory rise in insulin levels to normalize the insulin effect? If there is not enough insulin, glucose is high, but so are free fatty acids (FFAs). FFAs lead to atherogenic lipoprotein production, accelerate insulin resistance, promote ectopic fat deposition (which can be lipotoxic to the β -cell), and suppress anaerobic energy production in the heart. We also know that a relative lack of insulin can lead to increased TNF- α and ICAM-a, cytokines, O_2^- and PAI-1. In addition, high insulin levels in response to a reduced insulin effect reduce ischaemic preconditioning, and lack of insulin effect may reduce eNOS and vasodilation in response to ischaemia.

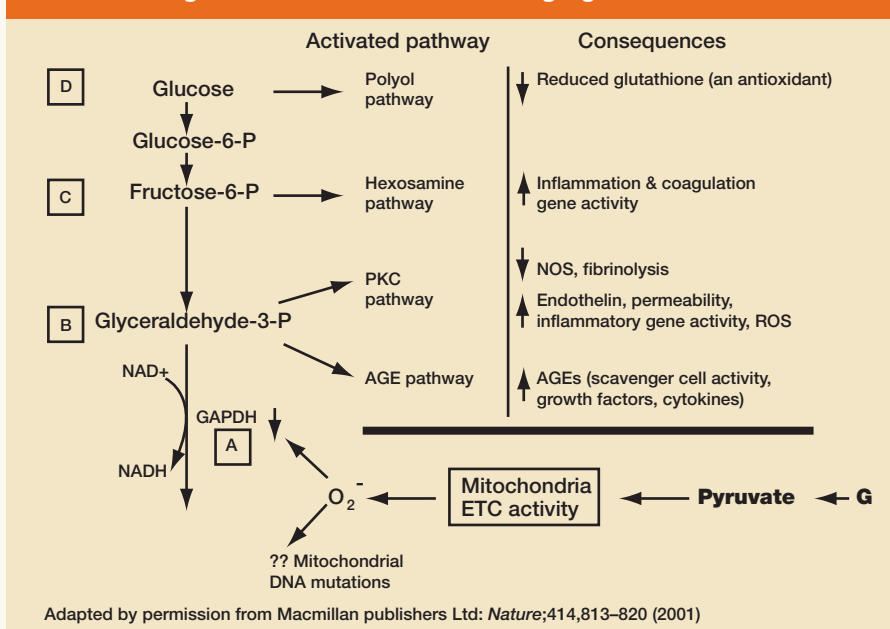
Finally, there may be genetic and environmental factors that predispose people to both glucose and CV disease. For example, smoking is a risk factor for hyperglycaemia, diabetes, dysglycaemia and CV disease, and cadmium, heavy metals and arsenic could have similar effects.

Can glucose lowering with insulin reduce CV events?

We do not know whether glucose lowering with insulin reduces CV events, and the only way to answer this question is through clinical trials. You cannot answer this question with epidemiology. The UKPDS reported a non-significant 16% relative risk reduction (RRR) in myocardial infarction (MI) in response to a policy of intensive glycaemic control with insulin and/or sulfonylureas (SU) versus conventional control ($p=0.052$). In the insulin-only subgroup, there was a 13% non-significant risk reduction for MI.⁶ Therefore, the UKPDS supports the hypothesis that glucose lowering with either insulin or SU may reduce CV events. In the Kumamoto study, a small number of people in the insulin arm showed a trend towards lowering CV events.⁷ Even in the UGDP study, there was a non-significant reduction of CV events in the variable insulin arm.⁸ The VACS DM pilot study, however, showed an increase in CV events with insulin as well as with SU.⁹ These type 2 diabetes studies support the hypothesis that glucose lowering with insulin or other drugs may reduce CV events. This hypothesis needs to be explicitly tested, with a design to precisely answer that question.

Finally, in the STOP NIDDM study, people with impaired glucose tolerance (IGT) were randomized to acarbose versus placebo. Those allocated to the acarbose arm had a 50% lower risk of a big composite outcome of CV events than those allocated to placebo.¹⁰ Even though acarbose is very unlikely to reduce CV events by 50%, this hypothesis-generating analysis suggests that glucose lowering may reduce CV events in people with IGT.

Figure 2. Cellular effects of a high glucose level⁵



Why insulin?

As many drugs are now available to lower glucose, what is so good about insulin? Although insulin clearly does reduce glucose levels, it also has other effects that may be good for the heart. For example, it reduces circulating FFAs effectively, it improves endothelial dysfunction, reduces inflammatory markers, promotes vasodilation, and has antithrombotic properties. Moreover, most clinical trials investigating glucose lowering have used insulin to achieve lower glucose levels and, as noted previously, have generally supported the possibility of a CV protective effect. Insulin is safe, really has only one side effect – hypoglycaemia (and if we can administer insulin optimally we will not even have that problem) – and is efficacious. There are no contraindications with insulin, and injections are virtually painless with the needles used today. Also, insulin is easily titratable, there is no maximum dose, and new formulations are getting easier and easier to use. We have many years of experience with this drug – more than 80 years; indeed, with the exception of drugs like digitalis and aspirin, there are few other agents with which we have as much experience.

Does insulin therapy preserve β -cell function?

This is an interesting hypothesis, and we do not know the answer, but we know that if glucose levels rise, there has to be some degree of underlying β -cell dysfunction, regardless of how much insulin it is actually producing. We also know that glucose and FFAs may be toxic to the β -cell. Therefore, if exogenous insulin is given to lower glucose levels, it may also reduce levels of a β -cell toxin. Of note is that there are both old and recent studies where people with diabetes who had their blood glucose levels intensively

controlled experienced either marked improvement,¹¹ or prolonged remission of their type 2 diabetes. Even the DCCT showed that the intensive insulin therapy group had higher glucagon-mediated C-peptide secretion than in the conventional therapy group,¹² suggesting that the insulin sparing may have slowed destruction of the β -cell. However, no clinical trials have really looked at whether insulin therapy preserves β -cell function.

What ongoing trials are testing the effectiveness of insulin in reducing CV events?

The ACCORD trial is an ongoing North American, National Institutes of Health (NIH)-funded trial. It involves more than 10,000 people with type 2 diabetes at high risk for CV events, randomized to two different target A_{1c} levels of either <6% or approximately 7.5%. Results are expected in 2009. The VA Diabetes Trial includes approximately 1,800 people, where again, patients are allocated to two different A_{1c} targets. In the ADVANCE Trial, more than 11,000 patients aged 55 and over have been randomized to gliclazide plus other agents targeting HbA_{1c} <6.5% versus standard care. The HEART 2D study of more than 1,300 patients is testing whether treatment with prandial insulin is superior to other insulin regimens with respect to CV events,¹³ and the ORIGIN trial has allocated people with early diabetes, impaired fasting glucose and IGT to insulin glargine, targeting a fasting glucose of ≤ 5.3 mmol/L versus standard approaches to dysglycaemia.

These studies are all expected to report by 2010, and are sure to change the way we approach dysglycaemia. They signify that we are really at the end of one CV

frontier and at the beginning of another that is focused on metabolic interventions and, if past experience is any indication, the research exploring this frontier is likely to raise many more questions than it answers.

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Editors:
Peter Rossing and
Ebbe Eldrup

Steno Education Center
Steno Diabetes Center
Niels Steensens Vej 2
2820 Gentofte
Denmark

www.stenodiabetescenter.com

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