Insulin resistance – the body's defence against caloric intoxication?

Novel hypotheses on the pathogenesis of type 2 diabetes have been put forward in recent years in which insulin resistance is proposed as a physiological defence mechanism against metabolic stress, especially for the heart.

Trond Methi
methi.trond@gmail.com
Per Medbøe Thorsby

The consequence of adaptive insulin resistance may be reduced risk of acute cardiovascular disease, but at the same time an increased burden on the other organs in the body, with an elevated risk of microvascular damage. Type 2 diabetes may be the price the body has to pay for survival in a caloric intoxicated state. But what is type 2 diabetes?

In the current paradigm type 2 diabetes is caused by an «inherited disposition, often in combination with overweight and decreased physical activity» (1). The disease is characterised by reduced sensitivity to the effects of insulin (insulin resistance) and reduced insulin production according to the needs of the body (beta cell failure), with resulting hyperglycaemia (2). The diagnosis is set when blood glucose reaches a certain level, for example measured by HbA1c ≥ 6.5 %.

Traditional pharmacological treatment aims to reduce glucose production by the liver (metformin), increase insulin production from beta cells (sulfonylureas) or add insulin through injections. It is well documented that intensive glycaemic control by the use of these mechanisms reduces the risk of microvascular disease in people with type 2 diabetes, as well as reducing the symptoms of hyperglycaemia (1).

Cardiovascular effects of intensive glycaemic control

People with type 2 diabetes have a two-fold increased risk of cardiovascular disease compared to the background population (3), and this is the most common cause of death (4). Epidemiological studies have shown an association between HbA1c and cardiovascular events (5), and a reasonable hypothesis has therefore been that a reduction in HbA1c will reduce cardiovascular risk, which is the case for people with type 1 diabetes (6). However, the evidence for this is weak for type 2 diabetes. Metformin has been shown to have a beneficial effect in overweight patients (7), whereas studies with intensive glycaemic control have shown either no significant effect on cardiovascular risk (8, 9), reduced mortality of early intensive treatment after long-term follow-up (10), or increased risk of cardiovascular death in patients with longer disease duration (11). These findings have led to a controversy on the value of intensive glycaemic control in reducing the risk of macrovascular events, and what the optimal treatment of type 2 diabetes should be.

> «The disease will seldom progress without a long-lasting caloric surplus caused by overeating and physical inactivity»

Caloric intoxication as a cause of type 2 diabetes?

New hypotheses on the pathogenesis of type 2 diabetes have been proposed in recent years, and may shed light on why the results of trials with intensive glycaemic control have been disappointing (12, 13)

Genetics is of significance in predisposing individuals to develop type 2 diabetes (2), but the disease will seldom progress without a long-lasting caloric surplus caused by overeating and physical inactivity. Initially, the body will handle caloric surplus by increasing fat storage in adipose tissues. This represents normal physiology as the body wants to conserve energy for leaner times. As long as there is available storage capacity, food intake may be continued without inducing metabolic disease. Some individuals have a considerable ability to store energy in subcutaneous adipose tissue, and may have a high BMI (body mass index) with normal blood glucose. In fact, only 25 % of people with BMI ≥ 40 kg/m^2 have type 2 diabetes (14). Others have lower capacity in subcutaneous adipose tissues and/or more dysfunctional beta cells, and will develop metabolic disease at a lower BMI. Approximately 15 % of people with type 2 diabetes have BMI ≤ 25 kg/m^2 (14). If the ability to store fat is inhibited in laboratory animals, they will develop type 2 diabetes more rapidly, even with lower body weight (15). This suggests that adipose storage capacity plays a role in disposing for development of the disease. Hypotheses regarding why some have more storage capacity than others have been reviewed previously (16).

Metabolic problems will arise however, when nutrients can no longer be stored in a safe manner. Newly published data indicate that ectopic storage of surplus energy outside of adipose tissues, especially in the pancreas, plays an important role in the development of type 2 diabetes (17). Type 2 diabetes is characterised by gradually increasing levels of glucose, lipids and free fatty acids in systemic circulation, which have toxic effects on cells and tissues in the body, so-called glucolipotoxicity: In other words, a caloric intoxicated state. Since this is a situation mankind has seldom encountered in the course of evolution, adequate defence mechanisms have not been developed to protect against the condition. The development of the disease is gradual, and may take many decades.

Insulin resistance as a protective mechanism

If the muscle tissues of the heart are overwhelmed by nutrients, they run the risk of collapsing metabolically, and will no longer be able to do their job, which is to keep the heart beating. One hypothesis is therefore that cardiomyocytes develop insulin resistance to protect themselves against this

fatal outcome (12, 13). Different degrees of insulin resistance may be induced in a similar manner in the liver, adipose tissue or skeletal muscle. When viewed thus, insulin resistance is not part of the pathogenesis of type 2 diabetes in the traditional sense, i.e. something which must be overcome by increasing doses of insulin, but rather a physiological defence mechanism against intracellular metabolic stress.

When insulin resistance is induced however, the beta cells respond by increasing insulin production to maintain blood glucose at a normal level. This enables the body to partition energy specifically between different organs, for example with increased relative insulin effect in adipose tissue and increased storage of energy, while the heart is better protected because increased exposure to insulin there is matched by reduced insulin sensitivity. For the body this is a choice between two evils, because the defence of the heart increases the burden on the other organs.

Although an insulin resistant heart is somewhat protected against caloric intoxication, the risk of cardiovascular disease is still elevated. This is due to the many other risk factors which are associated with metabolic disease, e.g. hypertension, dyslipidaemia and inflammation. These may cause atherosclerosis, which may lead to coronary disease, with an increased risk of myocardial infarction and cardiovascular death. Over time, metabolic overload may lead to ectopic storage of fat in the heart, so-called «fatty heart», which is harmful for its function. Furthermore, diabetic cardiomyopathy is associated with an increased risk of heart failure.

This pathogenesis contrasts with that of uncontrolled type 1 diabetes, in which there is also hyperglycaemia, relative hypertension and inflammation, and therefore increased risk of cardiovascular disease. In type 1 diabetes, however, the body does not suffer from caloric surplus and caloric intoxication, which is the case in type 2 diabetes. On the contrary, the cells are starving due to the absolute lack of insulin, and insulin resistance is therefore seldom observed.

Insulin resistance is controlled precisely by intracellular signalling mechanisms, and may be induced by many different conditions and stimuli, e.g. oxidative stress, glucocorticoids and hyperinsulinemia (18). There are several examples of insulin resistance being induced naturally in the body, such as during puberty and pregnancy, most likely due to prioritising energy for the development of the brain and the foetus respectively. It has been shown that reduced insulin sensitivity can be induced in healthy people of normal weight after only one month of overeating with a 40 % increase in caloric intake, and this happens before overweight is established (19). The condition is reversible upon subsequent caloric restriction, which shows that the system has a considerable degree of plasticity, and may be scaled upwards or downwards based on the energy balance in the body.

The problems arise, however, when caloric surplus is maintained over time. This provokes a higher degree of insulin resistance in metabolically stressed organs, among them adipose tissue. When the body reaches its maximum storage capacity, the upper limit of insulin resistance is also reached, and further beta cell compensation with increased insulin production is futile.

«Metabolic problems will arise when nutrients can no longer be stored in a safe manner»

Further hyperinsulinemia in such a case may be detrimental, for example for heart muscle tissue, because it will become subject to metabolic overload (12, 13). In light of this scenario, it has recently been proposed that «beta cell failure» in itself may also represent an adaptive physiological defence mechanism, where the beta cells do not necessarily collapse due to overwork, but reduce their insulin production actively to protect vital organs, and themselves, from overexposure to insulin (20). This is still only an hypothesis, but what is clear is that the beta cells are in a precarious position: They are set to monitor blood glucose and respond to increases in blood glucose by secreting insulin. When this no longer works because the effect of insulin has diminished, the resulting hyperglycaemia may also harm them. By reducing their uptake of glucose, and thereby their insulin production, acute beta cell death may be prevented. This may contribute to maintaining some level of insulin production, and may therefore delay an even more rapid progression to serious diabetes. If the beta cells in the body are subjected to chronic hyperglycaemia under experimental conditions, insulin production is reduced, but the beta cells do not die, because the condition is reversible upon release of the hyperglycaemic pressure (21). Whether the hypotheses around adaptive beta cell failure have any validity remains to be seen, but they are interesting because they are in radical conflict with the current paradigm on the role of the beta cells in the pathogenesis of type 2 diabetes.

Insulin therapy in insulin resistance?

Medical use of insulin plays a considerable role in the treatment of type 2 diabetes, and many trials have investigated long-term cardiovascular effects of insulin without any increased risk observed (8, 22). Insulin is, in other words, a commonly used and well validated treatment option, which many persons with type 2 diabetes depend upon to control their blood glucose (1).

What has not been studied sufficiently is the use of high insulin doses in overweight people with type 2 diabetes who are very insulin resistant, treatment resistant and have high cardiovascular risk. Overriding insulin resistance in such patients may force more energy into heart muscle which is already under metabolic stress (12, 13). The ACCORD trial was halted early due to increased mortality in the intensive glycaemic treatment arm (10). The highest risk of mortality was observed in people with high HbA1c who did not improve their glycaemic control despite an intensive treatment regime (23). Caution should be exercised in such patients, and perhaps a less intensive treatment goal should be accepted, rather than higher doses of insulin?

Lifestyle changes and caloric restriction

Since overeating and physical inactivity are the main drivers in the pathogenesis of type 2 diabetes, lifestyle changes are probably the best treatment option for the disease. Unfortunately, several studies have shown that sustained changes in lifestyle are challenging to achieve. In the Look-AHEAD trial, the observed effects of intensive lifestyle modifications did not result in reduced cardiovascular risk (24). The result was disappointing considering what one was hoping to achieve with lifestyle intervention. This negative result on «hard» endpoints in patients with longstanding diabetes indicates that the changes that occur with this disease are more complicated than what is suggested merely by the fact of being overweight and physically inactive.

On the other hand, several other positive outcomes were achieved, e.g. weight reduction, improved glycaemic control, reduced use/need for medication, reduction in sleep apnoea, improved quality of life and physical fitness/mobility. Furthermore, other smaller studies have shown good results for glycaemic control with lifestyle modifications (25, 26). In one trial with overweight patients with type 2 diabetes, a substantial effect on metabolism was observed, with near-normalisation of blood glucose after

only one week of caloric restriction (diet composed of 600 kcal/day) (26). After a total of 8 weeks, a reduction in the fat content of the liver and pancreas was determined, as well as an improvement in beta cell function and insulin sensitivity, and a reduction in HbA1c from 7.4 % to 6.0 %. The type 2 diabetic condition was thereby reversed by caloric restriction. Whether such a regime is realistic to achieve in practice is another matter, and here lies the challenge for the clinician and the patient.

It is also encouraging that large-scale randomized trials show that progression from impaired glucose tolerance (IGT) to type 2 diabetes may be reduced by up to 60 % with lifestyle intervention (27, 28). Bariatric surgery is another example where caloric restriction may normalise blood glucose rapidly and over time (29), and appears to have a beneficial effect on cardiovascular disease (30). One hypothesis is that this is caused by a reduction in caloric intoxication, which results in reduced insulin resistance and improved glucose homeostasis. In fact, it has been shown that a regime of caloric restriction similar to that achieved with bariatric surgery improves insulin resistance and beta cell function to the same degree as bariatric surgery in people with type 2 diabetes (31). These data indicate that caloric intoxication plays an important role in the pathogenesis of type 2 diabetes.

Type 2 diabetes develops due to a positive caloric balance over many years. Since insulin resistance appears early in the development of type 2 diabetes, and «beta cell decompensation» marks the initiation of a serious metabolic crisis, lifestyle modifications focusing on increased physical activity and caloric restriction, should be the cornerstone in the prevention, and probably also the treatment of the disease. People with type 2 diabetes should be informed that their disease is not necessarily progressive, but potentially may be reversed, at least in the early phase, if lifestyle changes can be accomplished. Again, the significance of individualised treatment of type 2 diabetes is underscored, where each person must be counselled and treated according to his or her clinical picture.

Trond Methi (born 1977)
MScPharm, PhD, Medical advisor, Lilly Diabetes.
The author has completed the ICMJE form and reports the following conflict of interest: He is employed by Eli Lilly.

Per Medbøe Thorsby (born 1964)
MD, PhD, Medical Head of Department at the Hormone Laboratory, Oslo University Hospital, Norway.
The author has completed the ICMJE form and reports the following conflict of interest: He receives personal fees from Norges Diabetesforbund, SanofiAventis, Bristol-Myers Squibb, Statens Legemiddelverk, and Antidoping Norge, outside the submitted work

References

1. Diabetes – forebygging, diagnostikk og behandling. Nasjonale faglige retningslinjer. IS-1674. Oslo: Helsedirektoratet, 2009.
2. Thorsby PM. Studies of candidate genes in overweight and diabetes mellitus. Oslo: Universitetet i Oslo, 2013.
3. Sarwar N, Gao P, Seshasai SR et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375: 2215–22.
4. Nwaneri C, Cooper H, Bowen-Jones D. Mortality in type 2 diabetes mellitus: magnitude of the evidence from a systematic review and meta-analysis. The British Journal of Diabetes & Vascular Disease 2013; 13: 192–207.
5. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405–12.
6. Nathan DM, Cleary PA, Backlund JY et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353: 2643–53.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854–65.
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–53.
9. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560–72.
10. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545–59.
11. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577–89.
12. Nolan CJ, Ruderman NB, Kahn SE et al. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. Diabetes 2015; 64: 673–86.
13. Taegtmeyer H, Beauloye C, Harmancey R et al. Insulin resistance protects the heart from fuel overload in dysregulated metabolic states. Am J Physiol Heart Circ Physiol 2013; 305: H1693–7.
14. Bays HE, Chapman RH, Grandy S. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract 2007; 61: 737–47.
15. Wang MY, Grayburn P, Chen S et al. Adipogenic capacity and the susceptibility to type 2 diabetes and metabolic syndrome. Proc Natl Acad Sci U S A 2008; 105: 6139–44.
16. Methi T, Thorsby PM. Hvorfor får ikke alle type 2-diabetes? Tidsskr Nor Legeforen 2014; 134: 2284–6.
17. Steven S, Hollingsworth KG, Small PK et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. Diabetes Care 2016; 39: 158–65.
18. Hoehn KL, Salmon AB, Hohnen-Behrens C et al. Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci U S A 2009; 106: 17787–92.
19. Brands M, Swat M, Lammers NM et al. Effects of a hypercaloric diet on β-cell responsivity in lean healthy men. Clin Endocrinol (Oxf) 2013; 78: 217–25.
20. Zaccardi F, Webb DR, Khunti K et al. Comment on Nolan et al. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. Diabetes 2015; 64: 673–686. Diabetes 2015; 64: e35–6.
21. Brunzell JD, Robertson RP, Lerner RL et al. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976; 42: 222–9.
22. Gerstein HC, Bosch J, Dagenais GR et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367: 319–28.
23. Riddle MC. Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010; 122: 844–6.
24. Wing RR, Bolin P, Brancati FL et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369: 145–54.
25. Aas AM, Bergstad I, Thorsby PM et al. An intensified lifestyle intervention programme may be superior to insulin treatment in poorly controlled Type 2 diabetic patients on oral hypoglycaemic agents: results of a feasibility study. Diabet Med 2005; 22: 316–22.
26. Lim EL, Hollingsworth KG, Aribisala BS et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011; 54: 2506–14.
27. Tuomilehto J, Lindström J, Eriksson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344: 1343–50.
28. Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393–403.
29. Mingrone G, Panunzi S, De Gaetano A et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015; 386: 964–73.
30. Eliasson B, Liakopoulos V, Franzén S et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. Lancet Diabetes Endocrinol 2015; 3: 847–54.
31. Jackness C, Karmally W, Febres G et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β-cell Function in type 2 diabetic patients. Diabetes 2013; 62: 3027–32.

Received 25 March 2016, first revision submitted 9 May 2016, accepted 19 May 2016. Editor: Ketil Slagstad.