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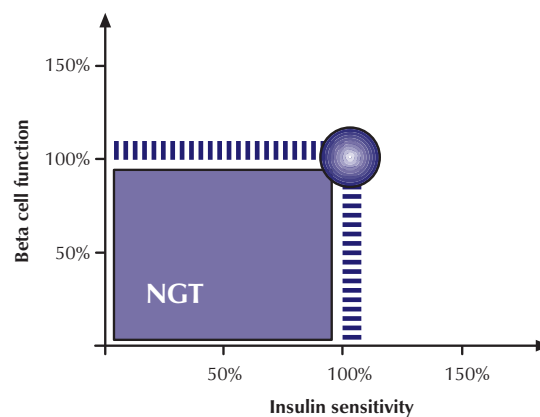
MICHEL P HERMANS

Before a patient develops overt type 2 diabetes mellitus, there is typically a prolonged period of pathophysiological change. In the common form of type 2 diabetes mellitus, there are years of insulin resistance, initially compensated by increased beta cell function, then impaired glucose tolerance develops, and finally type 2 diabetes. We know from studies such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Belfast study that loss of beta cell function and insulin resistance are usually relentless.^{1,2} Thus, therapy to reduce blood glucose has to be gradually increased with time for patients with diabetes. What is less well known is that every person has a different slope for beta cell function loss which intersects with insulin resistance. *Diabetes Vasc Dis Res* 2007;4(suppl 2):S7–S11
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There is a hyperbolic relationship between insulin sensitivity and beta cell function. Figure 1 shows this concept in pictorial form. Insulin sensitivity is represented on the x axis and beta-cell function on the y axis. A normal, ideal subject will have 100% insulin sensitivity and pancreatic beta cell secretory function will also be 100%. The combined area of x multiplied by y appears as a square shape in such a subject with normal insulin sensitivity and beta cell function and such area represents a subject's true, underlying beta cell function, adjusted for the prevailing insulin sensitivity. Such graphs can be used to represent a patient's requirement for glucose-lowering therapy (inversely in relation to functional area loss) and to cardiovascular risk (on the x axis).³⁻⁵

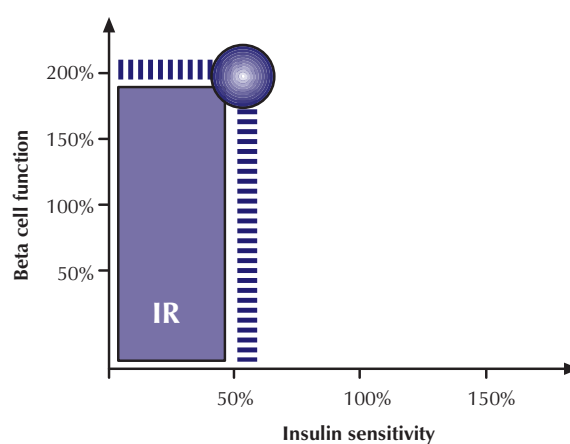
A patient with insulin resistance, metabolic syndrome and/or an enlarged waist circumference as a result of central adiposity will have the same area (if he has normal glucose tolerance) but the geometry will be quite different. It will take the shape of a rectangle standing on its smaller side (figure 2); the patient's endocrine pancreas will be secreting up to three or four times as much insulin in order to compensate for the decreased insulin sensitivity. This subject, while

Figure 1. Graph of normal glucose tolerance (beta cell function vs. insulin sensitivity)



Key: NGT = normal glucose tolerance

Figure 2. Graph of insulin resistance



Key: IR = insulin resistance

being at relatively high risk for cardiovascular disease, will usually have his cardiovascular risk underestimated since he will have normal glucose tolerance.

The reverse applies in subjects who exercise a lot. These subjects are usually lean, with high aerobic capacity, elevated relative or absolute skeletal muscle mass, are insulin-sensitive and have normal blood pressure and lipid profiles. They are at low risk for occurrence of cardiovascular disease or type 2 diabetes. In these subjects, the total area of the

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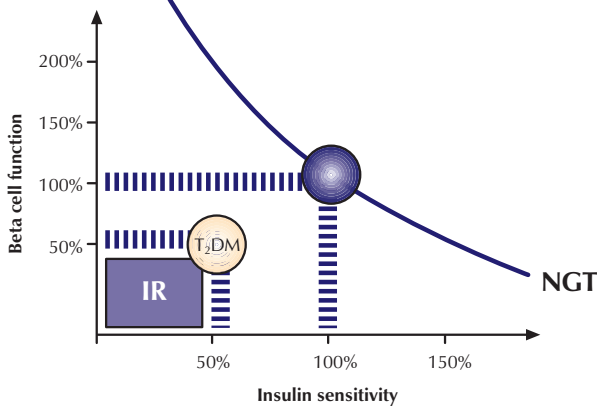
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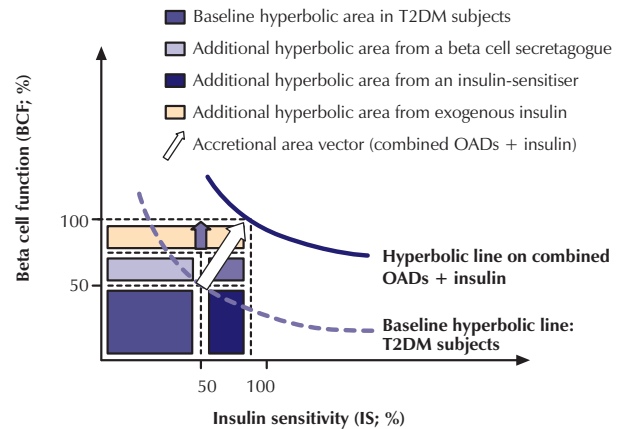
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Figure 3. Graph of type 2 diabetes (common form)



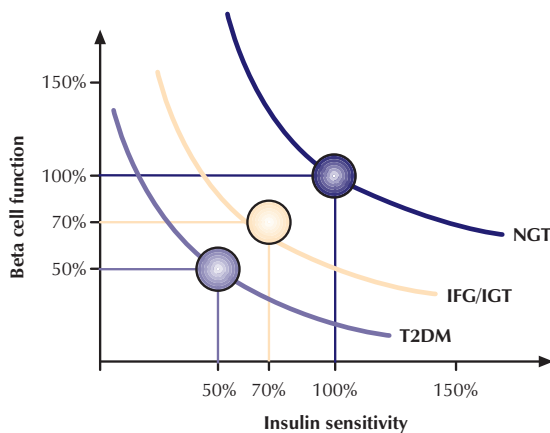
Key: NGT = normal glucose tolerance; IR = insulin resistance; T2DM = type 2 diabetes mellitus

Figure 5. Addition of insulin to oral antidiabetes drugs



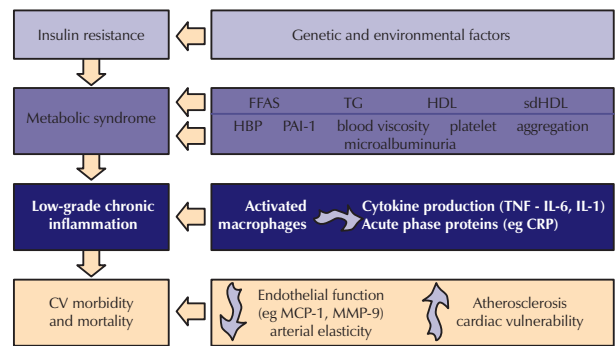
Key: T2DM = type 2 diabetes mellitus; OAD = oral antidiabetes drug; BCF = beta cell function

Figure 4. Hyperbolic relation between beta cell function and insulin sensitivity for diabetes, IGT and normal glucose tolerance



Key: NGT = normal glucose tolerance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus

Figure 6. Natural history of insulin resistance and cardiovascular disease



Key: FFAS = free fatty acids; TG = triglycerides; HDL = high-density lipoprotein; HBP = high blood pressure; PAI-1 = plasminogen activator inhibitor type 1; TNF = tumour necrosis factor; IL-6 = interleukin-6; IL-1 = interleukin-1; CRP = C-reactive protein; CV = cardiovascular; MCP-1 = monocyte chemoattractant protein 1; MMP-9 = matrix metalloproteinases

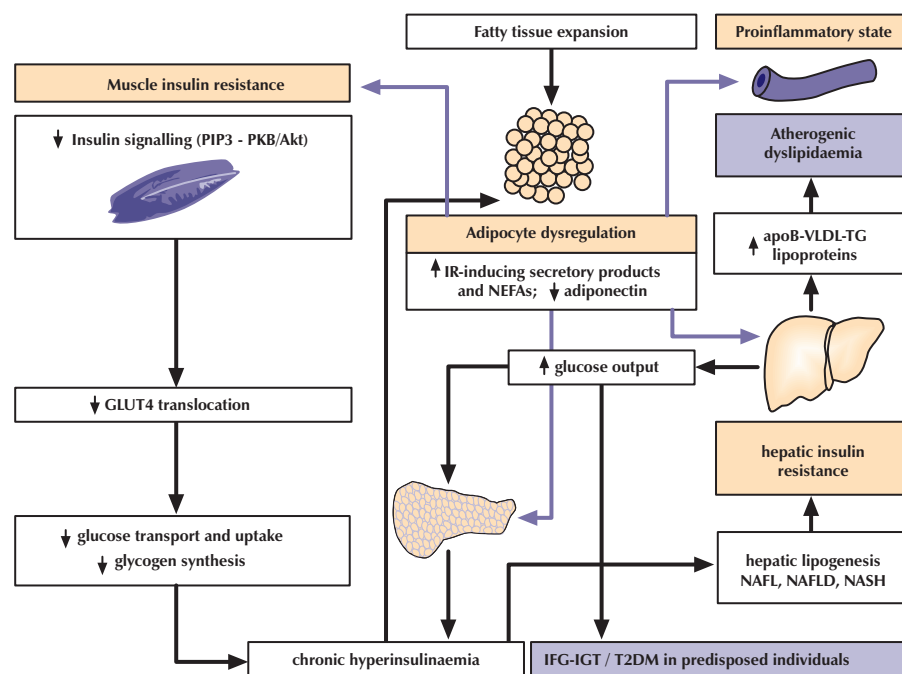
graph will be the same but the geometry will be different and there is a low risk for cardiovascular disease. All three of these subjects have normal glucose tolerance but they have different geometric shapes for this relationship between insulin sensitivity and beta cell function. Thus, the relationship between insulin sensitivity and beta cell function is a hyperbolic relationship, and x multiplied by y is a constant which represents the true underlying beta cell function adjusted for an individual's insulin sensitivity.

An average person with type 2 diabetes who is close to requiring lifelong insulin supplementation has about 50% of normal insulin sensitivity and his beta cell function is also about 50% of that of a normal subject. So beta cell function is in effect decreased by three quarters by this point, not half, as can be appreciated by looking at the functional area that determines glucose homeostasis (figure 3). Keeping the

shape of these curves in mind, low insulin sensitivity is related to cardiovascular risk whereas the total area is related to the individual's requirements for insulin and other glucose-lowering therapies throughout life.

Each subject has an individual slope of beta cell function loss and even in patients with diabetes the hyperbolic relationship remains. Those type 2 diabetes patients with normal insulin sensitivity have a low cardiovascular risk; therapy in those patients is mostly addressed to controlling their progressive hyperglycaemia and their advancing requisites for insulin replacement.

Patients with impaired glucose tolerance occupy an intermediate position between those with normal glucose tolerance and those with diabetes (figure 4). Most of them have already lost about one half of their beta cell function but they also often have increased cardiovascular risk, as

Figure 7. Paradigm of development of diabetes

Key: PIP3 = phosphatidylinositol (3,4,5) - triphosphate; PKB/Akt = protein kinase B/Akt; GLUT4 = type 4 glucose transporter; IR = insulin resistance; NEFA = non-esterified fatty acid; apoB = apolipoprotein B; VLDL = very low-density lipoprotein; TG = triglycerides; NAFL = non-alcoholic fatty liver; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steato-hepatitis; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus

many of them also exhibit abnormal insulin sensitivity. Before developing compensatory hyperinsulinaemia, insulin resistance and impaired fasting glucose, the subject who is prone to develop the common form of type 2 diabetes will initially have normal insulin sensitivity and beta cell function. Once he or she develops trunko-visceral obesity and insulin resistance, his cardiovascular risk will start to rise and it will remain elevated throughout his life, as a result of atherogenic dyslipidaemia, high blood pressure, a pro-inflammatory state and abnormal adipokine secretion. The pancreatic beta cells will lose their function (with different slopes for different individuals) but insulin resistance tends to remain fairly stable if a patient's weight (and hence trunko-visceral adiposity) remains fairly constant.

Glucose-lowering therapy for any type of diabetes mellitus can also be seen in terms of these hyperbolic relationships. Increasing beta cell function using orally active beta cell secretagogues adds an area to the vertical axis but insulin sensitivity is not increased and cardiovascular risk is usually not affected. There is a suggestion that glitazones may theoretically affect both variables and decrease cardiovascular risk but additional long-term prospective studies are needed. It also makes sense to provide simultaneous multiple therapies, including oral drugs, as soon as possible to patients since their concomitant use provides patients with a larger hyperbolic area (as shown by the vectorial gain in area in figure 5). However, most or all of these patients will end up with insulin sooner or later: those who require insulin earlier are those who lose their beta cell function more quickly

than the other ones. The steepness of the beta cell function loss slope, however, bears no relationship to cardiovascular risk.

The natural history of insulin resistance and cardiovascular disease

We know that cardiovascular risk increases inversely with loss of insulin sensitivity as well as with severity of metabolic syndrome score, but what determines the natural history? Figure 6 shows a typical progression of insulin resistance and cardiovascular disease.⁶ Insulin resistance is an underlying part of the metabolic syndrome phenotype, and that phenotype is likely to promote chronic low-grade inflammation of vascular walls, leading to cardiovascular morbidity and mortality. While assessing insulin sensitivity, not done routinely, establishing the presence of metabolic syndrome is easy to perform in a clinical setting. As regards the stage of low-grade chronic inflammation there is no agreement on what to measure – high sensitivity C-reactive protein might be a useful factor. Cardiovascular mortality and morbidity are all too easy to measure, unfortunately.

Insulin is seen principally as a hormone that promotes the entry of glucose through translocation and recruitment of type 4 glucose transporters (GLUT4) in skeletal muscle but there are many other effects that we should not forget when we discuss insulin resistance. It is really a multitarget hormone. For example, insulin exerts significant anabolic and anti-catabolic effects on skeletal muscle mass, and it is well established that many patients with central obesity have

reduced muscle mass (sarcopenia) and reduced muscle quality, with abnormal mitochondrial number, size and functionality.

What is the current paradigm? In most patients it starts with a sedentary lifestyle (figure 7). People increase their abdominal fat and this produces adipose tissue dysregulation, such as abnormal release of non-esterified fatty acids and dysregulation of adipokine release, including insulin-sensitising adiponectin. That will aggravate the insulin resistance in skeletal muscle induced by a sedentary lifestyle. As a result of chronic insulin resistance, not only will glucose entry be decreased but muscle mass will decrease over time. As GLUT 4 translocation decreases, so the pancreas will be induced to secrete more insulin (a state known as compensatory hyperinsulinaemia). Some individuals are able to increase insulin production for decades but that is probably not very healthy. Thus, while insulin itself is not atherogenic, some metabolic pathways in certain organs (such as the ovaries and the hepatocytes) will remain insulin-sensitive throughout life.

The major deleterious effect in this respect will be indirect and focused initially on the liver. While the hepatocyte will become insulin-resistant for some of its metabolic changes, resulting in glucose overproduction, other metabolic pathways remain insulin-sensitive in hepatocytes. Hepatic lipogenesis leading to steatosis, for example, remains insulin-sensitive even in insulin-resistant subjects. Hepatic glucose output will be increased, aggravating chronic hyperinsulinaemia and resulting in further liver steatosis as hepatic lipogenesis is a normal response to elevated portal insulin levels. Once the amount of stored liver fat becomes excessive, the liver will just transfer fat (in the form of very low-density lipoproteins, VLDL) to the next organ, which happens, rather unfortunately, to be the blood. This hydrogen-carbon export from liver to blood as VLDL is the underlying metabolic engine driving the atherogenic dyslipidaemia found in high prevalence in subjects with insulin resistance and/or metabolic syndrome, eventually resulting in low levels of high-density lipoprotein cholesterol (HDL-C), small and dense low-density lipoprotein (LDL) and elevated apolipoprotein B. Such an atherogenic dyslipidaemia will promote atherosclerosis and clinical event risk inasmuch as truncal fat expansion promotes a pro-inflammatory state. Chronic hyperinsulinaemia additionally promotes fat buildup in numerous ectopic sites.

While in most subjects the natural history begins with truncal fat expansion, it may also begin with isolated loss of skeletal muscle mass (sarcopenia) and/or oxidative aerobic capacity, another reason why exercise training aimed at increasing muscle mass and/or oxidative capacity is so metabolically relevant in these patients. Unfortunately, many patients will become aware of their cardiovascular risk only when a cardiovascular event takes place.

Therapeutic approaches

Therapies for type 2 diabetes are being designed to target every abnormality that may contribute to the development of long-term micro- and macrovascular complications. The inflammatory state and dyslipidaemia will be discussed

briefly here though there are many other therapeutic targets, such as lowering elevated blood pressure.

How can we address the pro-inflammatory state? The peroxisome proliferator-activated receptor α (PPAR- α) agonists are a class of drugs designed to promote liver fat oxidation while addressing ectopic fat storage in macrophages and plaque in both small and large blood vessels. Any type of LDL-C lowering and any type of HDL-C raising therapy is probably useful at this stage and therefore definitely worth consideration.

What about the small vessels and diabetic microvascular complications? Interestingly, the PPAR- α agonist fenofibrate has been shown in the FIELD study to decrease specific manifestations of microangiopathy in at least two target organs for long-term complications of hyperglycaemia, namely the retina and kidney (see Professor Zamboni's article in this supplement). What is the pathogenesis of diabetic microangiopathy? It can only occur in cells in which blood glucose is free to enter, that is in direct proportion to circulating blood levels, which explains why microvascular disease does not occur in organs such as muscle and liver in which glucose entry and its fate are tightly regulated.⁷

If the cell is not regulating its glucose entry, then massive amounts of glucose will enter the intracellular compartment once the person becomes diabetic and will then follow the glycolytic pathway. Glycolysis will then be accelerated, and this will eventually produce oxidative stress since the mitochondria will divert part of the enhanced electron transport into reactive oxygen species (ROS) production as a way to prevent excess voltage buildup in mitochondrial membrane. ROS-induced oxidative stress tends to damage mitochondrial DNA and/or nuclear DNA. Nuclear DNA will repair itself with a very efficient enzyme called poly(ADP-ribose) polymerase (PARP) yet while doing so, the repairing DNA enzyme will deactivate another enzyme, glyceraldehyde-3 phosphate dehydrogenase (GAPDH) that belongs to the glycolytic pathway whose activation by intracellular hyperglycaemia actually contributed to the enhanced ROS generation. This uphill retro-inhibition of the glycolytic pathway will paradoxically engender a pseudohypoxic signal to which the cell reacts by generating vascular growth factors and promoting new microvessel formation (neovascularisation).

Inhibition of GAPDH by PARP also brings about an intracellular accumulation of glycolytic intermediates involved in the four major pathways ascribed to the genesis of diabetic microangiopathy. Thus, fructose buildup within the cell will activate the sorbitol pathway; accumulation of fructose-6-phosphate will activate the hexosamine pathway while buildup of glyceraldehyde-3-phosphate will activate isoforms of protein kinase C as well as the advanced glycation end-product (AGE) pathway.⁸ This unifying mechanism also helps in understanding why glucose, because it enters freely into small-vessel cells of target organs, will accelerate the glycolytic pathway and ROS production, as well as all the major pathways for microangiopathic complications in direct proportion to hyperglycaemia in any type of diabetes.

At present, the mechanism(s) through which fenofibrate exerts its beneficial effects on diabetic microangiopathy remain(s) tantalisingly elusive. Experimental data show that

mice lacking PPAR- α develop an accelerated form of diabetic nephropathy,⁹ while fenofibrate has been shown to inhibit angiogenesis both *in vitro* and *in vivo*.¹⁰ Unravelling the mechanism of action of fenofibrate in reducing diabetic microvascular complications is also likely to give further clues about its pathogenesis and further leads for the development of new therapeutic strategies.

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