



Published in final edited form as:

*Curr Opin Biotechnol.* 2014 August ; 28: 165–170. doi:10.1016/j.copbio.2014.05.007.

## Systems Analysis and the Prediction and Prevention of Type 2 Diabetes Mellitus

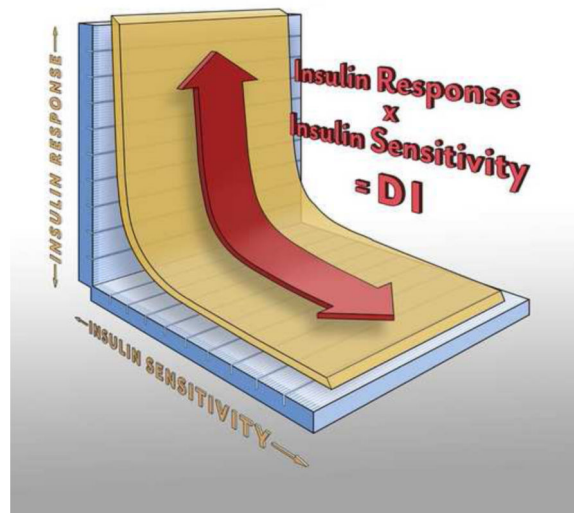
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### Abstract

Prevalence of Type 2 diabetes has increased at an alarming rate, highlighting the need to correctly predict the development of this disease in order to allow intervention and thus, slow progression of the disease and resulting metabolic derangement. There have been many recent “advances” geared towards the detection of pre-diabetes, including genome wide association studies and metabolomics. And although these approaches generate a large amount of data with a single blood sample, studies have indicated limited success using genetic and metabolomics information alone for identification of disease risk. Clinical assessment of the disposition index (DI) based on the hyperbolic law of glucose tolerance is a powerful predictor of Type 2 diabetes, but is not easily assessed in the clinical setting. Thus, it is evident that combining genetic or metabolomic approaches for a more simple assessment of DI may provide a useful tool to identify those at highest risk for Type 2 diabetes, allowing for intervention and prevention.

### Graphical Abstract



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## Type 2 diabetes: National and International Burden

Obesity has increased alarmingly in the United States and other westernized countries, and the trend is now worldwide (1). Obesity is the most significant risk factor for Type 2 diabetes, so that the prevalence of Type 2 diabetes has increased alarmingly. It is estimated that 18.8 million in the U.S. have diabetes, with another 7 million undiagnosed. The international burden has also increased, with an estimated over 4 million deaths due to diabetes per year. Thus there is a critical national and international need to prevent Type 2 diabetes. This has become a *cause celeb* in the United States, with the First Lady, Michelle Obama, leading the charge (2). Yet, it remains unclear how to approach the prevention of diabetes in the U.S. and elsewhere. Obviously the approach is to *predict* who is at greatest risk of the disease, and then invoke approaches to *prevent* the disease. In this article, We address the question of the possible role of systems analysis in this laudable and necessary goal.

## Systems Analysis in Biology

It is difficult to define systems analysis; it is something like jazz: “I can't define it, but I can tell when I hear it.” Thus, we are free to incorporate a convenient definition; to wit “Understanding biomedical systems by data-based mathematical modeling of their dynamical behavior. The objective of systems biology has been defined as the understanding of network behavior, and in particular their dynamic aspects, which requires the utilization of mathematical modeling tightly linked to experiment (3).” In addition, for convenience, we define two branches of Systems Biology: *Hypothesis generating*, versus *Hypothesis-based*. Of course these aforementioned definitions are arbitrary and are proposed merely for purposes of discussion.

## Prediction of Type 2 diabetes

Rather recently, there was little emphasis on prediction of disease. It was generally accepted that treatment, particularly with pharmaceuticals, would be limited to treatment of disease, rather than disease risk. Recent developments have changed this perception. Perreault et al. have recently reported that individuals with impaired glucose tolerance are at a significantly lower risk for Type 2 diabetes if they reverted to normal glucose tolerance from pre-diabetes even for a limited time (4). Thus, pre-diabetes is a progressive condition, and it is important to focus efforts on identification of those individuals who are at greatest risk for conversion to full-blown Type 2 diabetes, and intervene early.

Obesity is the primary risk factor for Type 2 diabetes. 80% of subjects with Type 2 are obese. Because of the panoply of conditions related to obesity (5), the latter has very recently been defined by the American Medical Association as a disease (6). It is very difficult to treat obesity and lifestyle changes (i.e., diet and exercise) usually fail. A few medicines have been approved for treating obesity (7), but the overall effects are limited in effectiveness. Of course, “metabolic (i.e., bariatric)” surgery is very effective to treat obesity and diabetes, but its use is limited to those at high risk, and is unlikely to be indicated except in very high risk situations (8). If obesity cannot be easily treated, is it possible to identify

those individuals particularly at risk for diabetes, and are there ways to intervene to prevent the illness? It has been clearly shown in various studies that intervention – lifestyle changes and/or insulin sensitizing medicines – can either delay progression to Type 2 diabetes, or prevent the disease entirely ((9), Figure 1). Can systems analysis help to identify those at risk for Type 2 diabetes? How successful have hypothesis-generating versus hypothesis-based approaches in the effort to detect so-called “prediabetics?”

## Hypothesis-generating approaches

### Genetics

There is strong evidence for a genetic basis for Type 2 diabetes from studies in twins and familial aggregation (10). Maturity Onset Diabetes of the Young (MODY) has been clearly attributed to coding mutations in either hepatocyte nuclear factor-1A (HNF1A) or glucokinase (GCK) genes (11). This syndrome accounts for only 1-2% of non-autoimmune Type 2 diabetes. Despite this early success, it has been much more difficult to identify genetic loci for Type 2 diabetes which account for a major fraction of the disease. In fact, approximately 64 loci have been identified from GWAS studies, but these variants have overall a minor effect on diabetes risk (12). In fact, TCF7L2 has the largest identified risk – a factor of about 2 – and other identified variants have less. Therefore there is a good fraction of demonstrated heritability of Type 2 diabetes which remains unaccounted for by known genetics (“missing heritability”), although some may be accounted for by epigenetic changes which occur, possibly *in utero*. Schmid et al. have reported that adding genetic information does not increase ability to predict Type 2 diabetes beyond that which can be done by clinical risk scores (13). Therefore, it is not at this time appropriate to recommend using genetic information to identify prediabetics beyond what can be gleaned from clinical information. The original optimism regarding the possibility of using genetic analyses to identify those at risk for Type 2 diabetes has not been borne out; however, one very interesting outcome has been the realization that the majority of the variants identified for diabetes risk are associated with insulin secretion or degradation, not with insulin resistance. This has supported the focus on defects or changes in insulin secretion and metabolic clearance of insulin as progenitors of diabetes (see below).

### Metabolomics

Recently there has been a flood of information regarding the use of metabolomics to identify those at risk for Type 2 diabetes. The overall concept is that if the approximately 8000 small biological molecules in bodily fluids (blood, urine, CSF etc.) could be accurately measured, they would be useful indicators of and potentially predictors of disease, including diabetes. It is a reasonable assumption that if there are pathways which are particularly important in diabetes development, changes in said pathways would be reflected in the levels of specific biomarkers in bodily fluids including blood. Once specific indicators are identified, it is reasonable to identify the pathways, and possibly the fluxes or metabolic steps within such pathways which might lead to diabetes.

Extensive study of metabolomics patterns have identified a variety of possible risk factors (14-15). These include lipid molecules, including free fatty acids, bile acids, and in

particular amino acids – particularly the branched chain amino acids. At present, because a large number of possible risk factors have emerged from metabolomics studies, it is not yet possible to definitively argue that one or more suggested factors will finally be available to confidently predict risk. The use of spectroscopy to measure a large number of factors in individuals at risk of diabetes, as well as those with diabetes, will continue to provide potential metabolic markers. It is not possible at this juncture to identify compounds which will emerge as the greatest predictors. Clearly, however, the metabolomics approach is fundamentally an hypothesis free (or hypothesis generating) approach, as an agnostic perspective is generally taken, in which any and all compounds may be measured and may predict risk—either predictably or surprisingly. Importantly however is the bias in most metabolomics studies in which the metabolic mechanisms potentially related to compounds in blood are most likely to be related to function of tissues prevalent at large mass in the body – for example the liver, muscle and/or adipose tissue. Those tissues are insulin resistant in the prediabetic and diabetic states. We can thereby suggest that the metabolomic approach will identify a metabolic signature which is closely aligned with insulin resistance in the prediabetic state – a condition which is likely to be related also to increased adiposity. It seems less likely that more latent defects in the prediabetic state such as defects in beta-cell function might be harder to detect with the metabolomic approach. Yet, it is the latter defect which may well be the most important and sensitive indicator of prediabetes (16). The potential of the metabolomic approach overall may lie in its putative limitation in detecting beta-cell defects (see below).

Recently, a metabolomics success story has emerged from the work of C. Newgard and others. They specifically identified the branched-chain amino acids as being associated with insulin resistance of obesity in a variety of animal models, as well as in humans (17-19). Insulin resistance is a primary risk factor for Type 2 diabetes, and therefore it has been suggested that branched chain amino acids can be used as a predictor. In fact, Wang and colleagues exploited the Framingham data base to examine the use of the branched-chains in this context. They examined a limited population in which a fraction of high risk individuals studied converted from a high risk state (obesity, family history) to overt Type 2 diabetes over 12 years. They reported that the observed probability of converting to diabetes was 5-fold greater in those with the lowest versus the highest overall concentrations of branched-chain amino acids. While this number appears compelling, when the same metric was applied to the overall Framingham population, the risk was considerably lower – the odds ratio of converting to Type 2 diabetes was approximately two-fold.

While the metabolomics approach has great potential for identifying those at risk for Type 2 diabetes based upon the measurement of small molecules in blood, it may be limited by the physiological importance of these molecules. In general, branched-chain amino acids are indicators of insulin resistance *per se*; however insulin resistance is not the only defect leading to Type 2. Genetic studies as well as epidemiological studies (20, 21) have demonstrated convincingly that a beta-cell defect is a critical factor in Type 2 development. Therefore a resistance-based defect may not be able to be a strong predictor of the disease as the influence of the beta-cell may not be reflected in the metabolomic measurement. Whether there is a small molecule or group of molecules which reflect subtle beta-cell defects which may presage diabetes remains to be determined.

## Hypothesis-based approaches

Despite the excitement and immense investment in genetics (and epigenetics) and “omic” research (particularly metabolomics) the hypothesis based approaches account for our understanding of the pathogenesis of Type 2 diabetes. If the latter supposition is true, then hypothesis based research should continue to be pursued.

### Secretion versus action

For decades, whether insulin resistance or defects in insulin secretion was responsible for Type 2 diabetes was debated (22, 23). Several decades ago we suggested that this dialectic could be resolved only by considering the relative importance of insulin secretory function in the context of insulin resistance. We considered that in an insulin resistant state, occasioned either normally (e.g., in pregnancy, puberty, normal weight gain) or pathologically (e.g., obesity, infection, PCOS), would be compensated in a defined way by enhanced insulin levels in the blood. In fact, we proposed for the first time that the relationship between insulin sensitivity (the inverse of insulin resistance) and insulin response be expressed quantitatively as the following **hypothesis**, represented by a quantitative equation (24):

### Insulin sensitivity × Insulin Response = the Disposition Index (DI)

In which the DI is considered a characteristic value for a given individual in the normal state. Thus, by this so-called “Hyperbolic Law of Glucose Tolerance (25)” a reduction in insulin sensitivity would be compensated by an increase in insulin sensitivity, such that DI remained relatively constant for a given individual. By this conception, we proposed that an individual *at risk for Type 2 diabetes* the failure of the pancreatic islets to adequately compensate for insulin resistance would be reflected in a reduced disposition index. Inadequate compensation should be observed in those at risk for diabetes. More recently, it has been demonstrated that although this hyperbolic relationship is maintained across ethnic groups in healthy individuals, there are distinct ethnic differences in the contribution of insulin sensitivity vs insulin response to maintain normal glucose tolerance (Figure 2) (26). It is of interest that the above Equation represents a specific hypothesis; it was based upon considerations of the ability of a closed-loop system to regulate an important variable, but it was by no means proven initially. However, cross sectional data (27, 28) confirmed the hyperbolic relationship between insulin sensitivity and insulin secretion; in addition Kahn et al. examined the relationship in a population of normal individuals and demonstrated that DI was normally distributed. Of course it was assumed in the original conception that insulin sensitivity changed in response to changes in lifestyle; however it is also possible that hyperinsulinemia *per se* causes a reflexive change in insulin action at insulin sensitive tissues (muscle, liver and fat) such that insulin level should be the independent variable and insulin action the dependent one (29, 30). At this juncture whether the so-called “insulin resistance syndrome” is driven by oversecretion by the beta cells of the pancreas remains suggested but unproven, but there is evidence that hyperinsulinemia itself can down regulate insulin action. The most likely scenario is that *both* mechanisms are at play – resulting in a closed loop system regulating the blood glucose which compensates appropriately for

insulin resistance or hyperinsulinemia, and resulting in the normal blood glucose concentration.

An important question is the mechanisms underlying the hyperbolic relationship. We have shown that induction of insulin resistance with a moderate elevated fat diet causes a reflexive reduction in metabolic clearance rate of insulin (at the level of the liver) as well as a time-dependent increase in beta-cell sensitivity to glucose. It is reasonable to assume that the signal to the pancreas which is responsible for the increased secretion would be glycemia itself; however we have shown that there is no change in fasting glycemia or in 24-hour glycemia which could be responsible for the increased beta-cell function in an insulin resistant state. We have carefully searched for the signal which provokes the pancreatic response; we have ruled out GLP-1, cortisol, as well as growth hormone. Recently, we discovered that free fatty acids (FFA) increase nocturnally (31), and that the nocturnal increase in FFA is enhanced in the insulin resistant state. In fact, we propose that nocturnal FFA is the signal which enhances beta-cell response in an insulin resistant situation, and that this ability of FFA may be reduced when diabetes risk is elevated.

### Diabetes prediction

As discussed, it remains difficult to predict Type 2 diabetes in advance with genetics, and metabolomics is also an imperfect mechanism as changes observed appear to reflect insulin resistance, rather than beta cell function. But the DI reflects the ability of the pancreatic beta cells to compensate for insulin resistance. We expect that this compensatory ability is reduced in those at risk for Type 2 diabetes. Given, this, does the DI provide a means to predict Type 2 diabetes in those at risk for the disease? Population studies have confirmed that the DI value in an individual is an excellent predictor of later conversion to diabetes (21). In a study of members of the Pima Nation by Weyer, et al., individuals with normal glucose tolerance were observed for a 5 year period to determine which developed impaired glucose tolerance, and which developed diabetes (32). As shown in Figure 3, the group with a better DI value had no reduction in glucose tolerance over the observation interval; those with lesser DI (but also normal glucose tolerance) became glucose intolerant and then developed diabetes. Thus, in the Pimas DI was a strong predictor of conversion to Type 2 diabetes. In fact, the risk of conversion to diabetes was 20-fold higher in those in the top decile of DI value compared to the lowest decile of DI. Therefore, DI is a strong predictor of conversion of normal glucose tolerance to diabetes (33); a much stronger predictor than known genetic or metabolomics signals. The ability of the DI to predict diabetes has been confirmed in the “ACT NOW” study, performed by DeFronzo and his colleagues, who reported that in a high risk population, risk of conversion to Type 2 diabetes over a 2.5 year period was greatest for the Disposition Index, calculated from the OGTT (34).

Of course it remains considerably more difficult to estimate DI from a clinical procedure than doing a genetic analysis or measuring analytes from blood. What is needed is a surrogate approach to measure DI from blood samples, or from a simpler clinical procedure than is now available.

## Concluding Remarks: Systems Analysis and Diabetes Prediction

Diabetes is increasing nationally and internationally, and is now a highly significant public health problem. Lifestyle changes and pharmaceutical intervention has been demonstrated to at least retard the development of the disease, if not to prevent it altogether. Yet, it is still not possible to identify those individuals most at risk for the illness who deserve the most attention for prevention. Systems analysis in its various guises is being used to address this problem. As we have seen, hypothesis-free approaches such as genetics and “omics” have been proposed as excellent approaches to identify at-risk individuals. Success however, remains to be proven using these approaches. Alternatively, the hypothesis based “law of glucose tolerance” approach, using the disposition index has been proven to be a very powerful (in fact the most powerful) predictor of Type 2 diabetes. But, methods are not yet available to assess DI easily, in a form that can be available in the clinic. Thus, it is an important goal to measure DI easily, either with simple measurement, or possibly using modern methods of “omic” assessment. In this sense, then, hypothesis-free and hypothesis-based methods might come together to identify those at highest risk for Type 2 diabetes mellitus so that intervention and prevention can be used worldwide.

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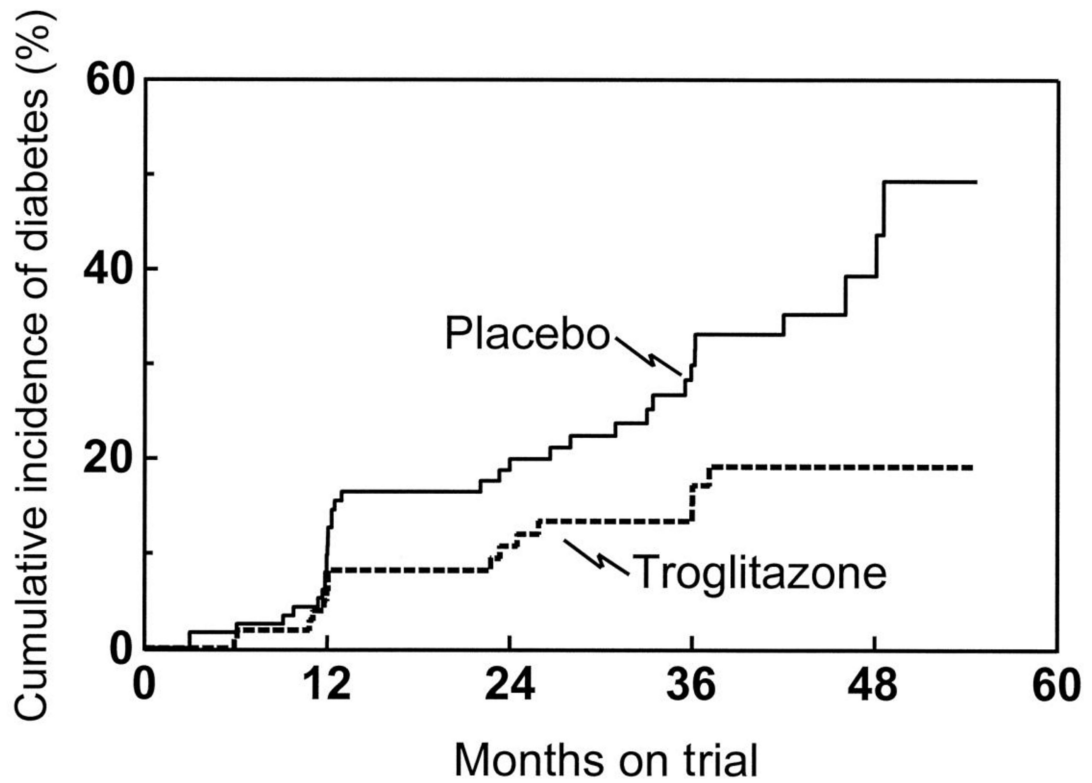
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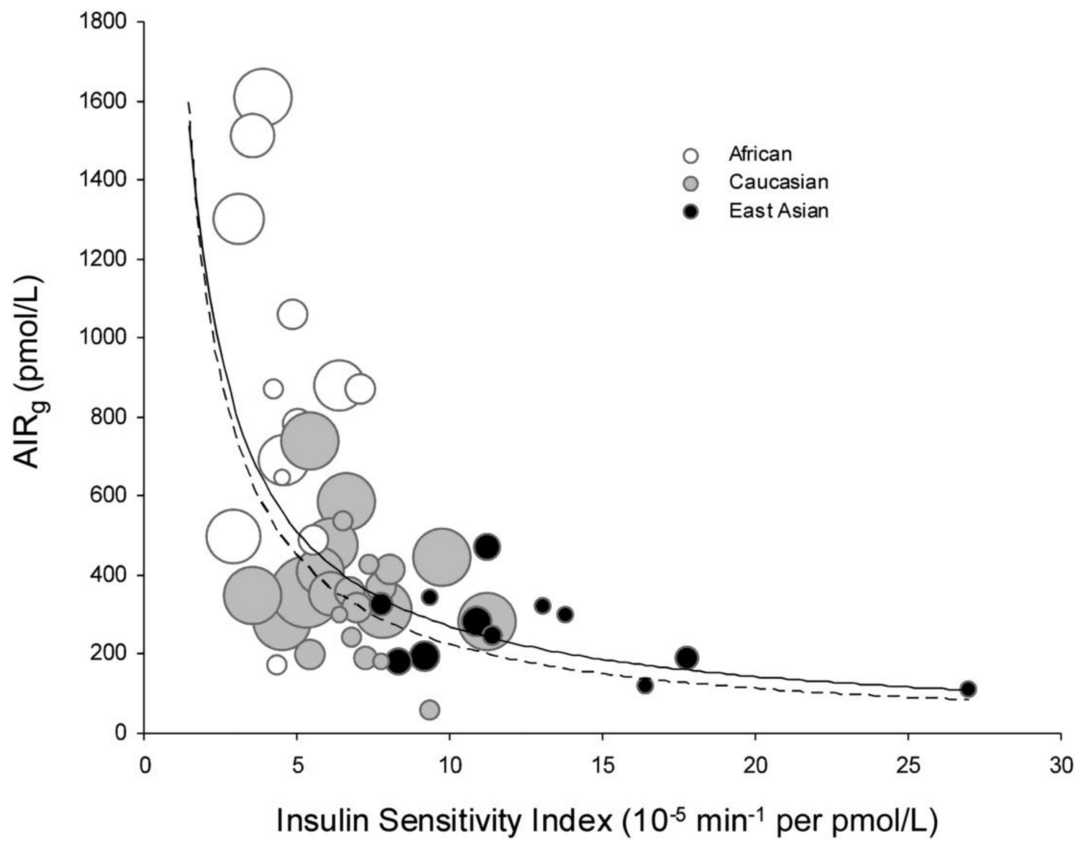
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### Highlights

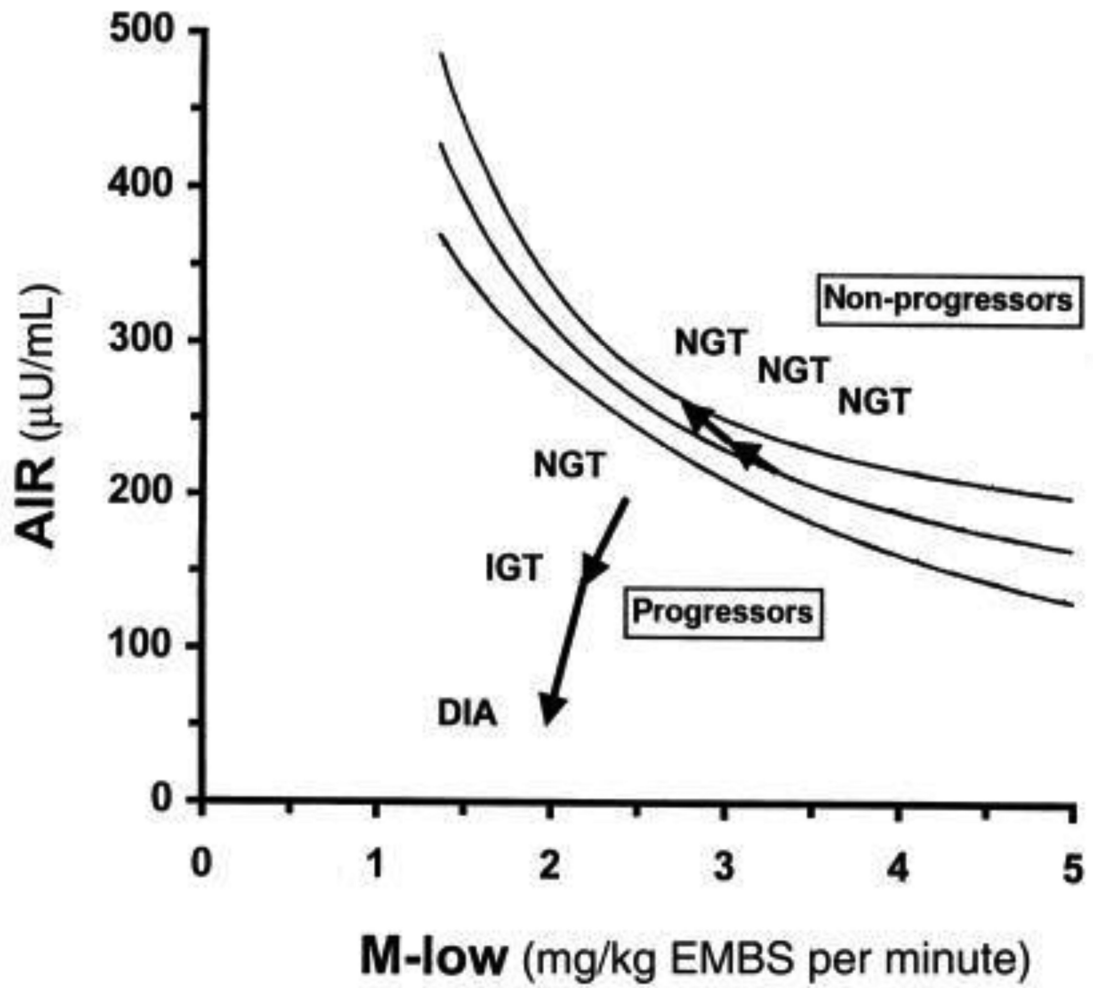
- Prediction of Type 2 diabetes allows intervention which slows disease progression.
- Genetic and metabolomic approaches have had limited success in diabetes prediction.
- Hypothesis-based hyperbolic law of glucose tolerance (DI) predicts Type 2 diabetes.
- It is important to easily measure DI in a non-clinical setting.
- This may be possible by merging hypothesis-generating and hypothesis-driven approaches.



**Figure 1.** Cumulative incidence rates of type 2 diabetes in women with previous gestational diabetes who were treated with either placebo or troglitazone. The rate in the troglitazone group was significantly lower than the rate in the placebo group ( $P = 0.009$ ). From [9].



**Figure 2.** Ethnic differences in the relationship between insulin sensitivity and insulin response. From [26]



**Figure 3.** Changes in insulin response relative to changes in insulin sensitivity in Pima Indian subjects. Those with a higher DI retained normal glucose tolerance (NGT) (nonprogressors) whereas those with a lower DI deteriorated from NGT to impaired (IGT) to diabetic (DIA) (progressors). From [32].