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Validating a Dimensionless Number for Glucose Homeostasis in Humans

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Abstract

Understanding type 2 diabetes is challenged by the diversity of patient phenotypes. Translating data across species and among individuals is a barrier for understanding the genetic loci that underpin this multifactorial disease. Dynamic scaling, based upon dimensional analysis, is a common technique in engineering used to translate data among different systems. The objective of this study was to gain insight using dimensional analysis into the relative changes in insulin production capacity versus insulin-dependent glucose metabolism in patient groups that represent distinct stages of disease progression. A dimensionless number was derived using variables involved in the production of insulin and in the sensitivity of glucose metabolism to insulin. The resulting dynamic scaling relationship was validated against patient data obtained for over 2000 individuals that range in phenotype from normal to severe type 2 diabetes. Individuals were identified in the third National Health and Nutrition Evaluation Survey. Patient groups clustered in different regions based upon the severity of clinical symptoms. The cross-sectional comparison among patient groups shows that progression from normal to clinical onset of type 2 diabetes exhibits a non-linear change in the ratio of insulin production to insulin-dependent glucose metabolism: normals are balanced, pre-diabetic individuals exhibit an increase, and individuals with clinical type 2 diabetes exhibit a decrease in this ratio. This dimensionless number provides a method for discriminating between patient groups from first principles. By analogy with other dimensionless numbers, this number may be used to monitor basic physiological variables responsible for glucose homeostasis. In addition, a similar dynamic trajectory to the clinical populations could provide a criterion for selecting relevant animal models for diabetes.

Keywords

clinical tests; hyperbola paradigm; insulin action; insulin secretion; diabetes mellitus; glucose-tolerance test; National Health and Nutrition Examination Survey; translational research

1 Introduction

Type 2 diabetes is a multifactorial disease embodied by elevated fasting and post-prandial blood glucose; impaired insulin sensitivity in muscle, liver and adipose tissue; and impaired

pancreatic function.^{13,14} The multifactorial nature of type 2 diabetes suggests that individuals, who exhibit similar phenotypes, may harbor multiple pathogenic lesions. Pathogenic lesions manifest themselves as variations in functional responses to common stimuli. Recent technological advances in molecular biology coupled with relevant animal models provide insight into these functional responses that underpin nutrient metabolism and glucose homeostasis within a biological system.³⁸ However, a significant barrier to progress in understanding this disease is the difficulty in translating data across species and among individuals.³⁵

In engineering, extrapolating experimental finding among dynamic systems is achieved via dynamic scaling, a technique based upon dimensional analysis.¹⁶ Dimensional analysis is a powerful approach to assess the importance of various components of a dynamic system and to create an expectation of how similar systems should behave.³ For instance, the Thiele modulus, a dimensionless ratio between rates of reaction and diffusion in porous media, has been used to predict the efficacy of therapeutic antibodies in tumor spheroids.⁴⁰ In the cardiovascular area, the Reynolds and Womersley numbers provide a theoretical basis for understanding the physical phenomena associated with hemodynamic flow fields.⁴¹ *In vitro* model systems, created using similar hemodynamic scales, have been particularly helpful in understanding the biological mechanisms that underpin observed correlations between flow patterns and clinical implications, such as the association between shear stress and atherosclerosis.³¹ As illustrated by these examples, providing an expectation of system behavior, in the form of a model, can be particularly valuable in the study of biological systems, where study *in vivo* may be particularly challenging.

A recent report from the National Research Council identifies a need for deeper integration of theory into biological research.³³ In this context, theory encoded in a computable form (i.e., a mathematical model) facilitates quantitative validation of the theory against data. Mathematical models have long played a prominent role in understanding and mitigating the underlying pathophysiology of type 2 diabetes (e.g.,^{5,26,29}). The types of mathematical approaches vary widely and play different roles in improving patient outcomes. However, state-of-the-art approaches for risk assessment and patient stratification in diabetes are largely based upon correlative metrics (e.g.,^{17,18,1,24,37}). Mechanistic insight into the underlying pathophysiology specific to an individual, even using a simple relationship, may be particularly helpful for assessing risk and identifying biomarkers. The objective of this study was to gain insight into underlying biological phenomena responsible for glucose homeostasis using dimensional analysis. The dimensional analysis provided an index for quantifying the relative changes in insulin production versus insulin-dependent glucose metabolism in clinical groups that represent different stages of the disease. In addition, this index was derived from measurements typically used in assessing glucose homeostasis in large-scale clinical populations.

2 Materials and Methods

2.1 Derivation of a Dimensionless Number

Dimensional analysis was applied following the “Buckingham II theorem.” This theorem states that: *the functional relationship among q quantities, whose units may be given in*

terms of u fundamental units, may be written as a function of $q - u$ dimensionless groups (the Π 's).⁷ Six variables were selected to represent important system characteristics of glucose homeostasis. The six variables and their corresponding fundamental units are shown in Table 1. Five of the six variables are derived from a steady-state mass balance on insulin. Changes in the concentration of insulin (C_{Ins}) are regulated by the rate of production (i.e., $\alpha \cdot BCM/V$) and rate of disposal (i.e., $k_d \cdot C_{Ins}$). The sensitivity of glucose metabolism to changes in insulin is characterized by the sixth variable, S_{Ins} . The six variables are comprised of four fundamental units: length, time, mass, and moles. Two dimensionless variables were created from these system variables following from the Buckingham Π theorem. Each dimensionless variable was based around one of two core variables, S_{Ins} and BCM . These two variables are thought to be altered in disease. A reduction in insulin sensitivity is thought to occur in patients with type 2 diabetes while a reduction in beta cell mass occurs in patients with type 1 diabetes. Each core variable was combined with the remaining variables. The power associated with each non-core variable was determined such that the product of the core variable and non-core variables gives rise to a dimensionless number. The first dimensionless number based upon S_{Ins} was:

$$\Pi_1 = \frac{S_{Ins}}{k_d \cdot V} \quad (1)$$

The second dimensionless number based upon BCM was determined to be:

$$\Pi_2 = \frac{\alpha \cdot BCM}{C_{Ins} \cdot k_d \cdot V} \quad (2)$$

However, values for the variable k_d are not typically measured in large-scale clinical trials. The dimensionless numbers were combined to eliminate k_d as follows:

$$\frac{\Pi_2}{\Pi_1} = \frac{\alpha \cdot BCM}{C_{Ins} \cdot k_d \cdot V} \cdot \frac{k_d \cdot V}{S_{Ins}} \quad (3)$$

Further simplification yields the form of the dimensionless number used in the analysis:

$$N_D = \frac{\alpha \cdot BCM}{C_{Ins} \cdot S_{Ins}} \quad (4)$$

2.2 Clinical Data

The dimensionless number N_D was reformulated in terms of variables commonly used in large-scale clinical trials ($\tilde{N}_D$). Values for $\tilde{N}_D$ were calculated based upon patient-specific data obtained from the third National Health and Nutrition Examination Survey (NHANES III).¹¹ Conducted from 1988 until 1994 in the United States, the NHANES III reports survey results for over 3,600 measured variables in approximately 33,000 individuals. Individuals were filtered from the entire NHANES III cohort based on self-reported fasting greater than 7.5 hours and a valid oral glucose tolerance test (OGTT). For our analysis, N_D was

calculated from the survey results for blood testing, body composition, and OGTTs in adults over 40. The clinical characteristics of the individuals identified in the database range in disease severity from normal to severe diabetic. In addition, each of these individuals were classified into one of three categories based upon the criteria specified by the American Diabetes Association (ADA) for diagnosis of type 2 diabetes (i.e. fasting glucose ≥ 126 mg/dl or plasma glucose following OGTT ≥ 200 mg/dl).^{2,20} The categories were defined as diabetic; pre-diabetic, which included impaired glucose tolerance (IGT) and impaired fasting glucose (IFG); and normals. In addition, individuals identified as exhibiting the clinical symptoms of type 2 diabetes were subdivided into known diabetics (i.e., a health care provider had told them that they have diabetes) and unknown diabetics (i.e., these individuals have not been diagnosed with diabetes). The variables extracted from the NHANES III database that were used in the analysis are highlighted in Table 2. The entire dataset used in the analysis is found in Table S3 (see supplemental material on-line). Manipulation of the clinical data was performed using R/Bioconductor (see on-line supplement for sample R script). The two-dimensional probability density function was estimated using kernel density estimation.²¹ Kernel density estimation is a non-parametric smoothing technique used to estimate probability density functions from independent samples drawn from the population of interest. While it shares some similarity with estimating a density function using a normalized histogram, the kernel method exhibits less bias in estimating the density function. The bias in a histogram estimator with a bin width h is of order h . In contrast, the kernel is centered at each point and, by using a symmetric kernel, yields a leading bias term for the kernel estimate of order h^2 . Default values for the bandwidth were used. A Student's t-Test, with a Welch correction for different degrees of freedom between groups, was used to determine the confidence level associated with the difference between mean values. A p -value less than 0.05 was considered statistically significant.

2.3 Classification Methods

As an alternative to ADA criteria, the glucose metabolism and insulin production metrics can be used to classify individuals into severity groups. The accuracy of these metrics for classifying individuals was estimated using an algorithm developed for quantifying significant differences between non-parametric probability density functions.²³ This algorithm considers two non-parametric probability density functions: a function describing the real group, $f_R(x, y)$, and a function describing a second group, $f_M(x, y)$. One would classify a new observation, x_n and y_n , as being drawn from the real group if and only if:

$$p \cdot f_R(x_n, y_n) - (1 - p) \cdot f_M(x_n, y_n) \geq 0, \quad (5)$$

where p is the prior probability that an unclassified observation is from the real group. If the relationship shown in equation 5 is less than zero, the probability that the observation (x_n, y_n) would be misclassified as being from the second group is $(1 - p)$. This criterion can be expressed in terms of a continuous function:

$$E(x, y, f_R, f_M) = \begin{cases} 0 & \text{if } p \cdot f_R(x, y) - (1 - p) \cdot f_M(x, y) \geq 0 \\ 1 & \text{if } p \cdot f_R(x, y) - (1 - p) \cdot f_M(x, y) < 0 \end{cases} \quad (6)$$

The fraction of the real population that can be misclassified as part of the second population (F_{Mis}) is then:

$$F_{Mis} = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} E(x, y, f_R, f_M) \cdot f_R(x, y) dx dy. \quad (7)$$

3 Results

3.1 Derivation of Dimensionless Number

By drawing an analogy to the Reynolds number as being ratio of inertial to viscous forces, I postulated whether a similar relationship could be related to glucose homeostasis. Common wisdom is that Type 1 diabetes is related to a loss of insulin production while Type 2 diabetes is related to a loss in insulin-dependent glucose metabolism. Health would therefore be when these “forces” are balanced. A dimensionless number was developed from first principles to represent this theory that insulin production and insulin-dependent glucose metabolism is balanced in health and becomes imbalanced in disease. The dimensionless number, N_D , was derived in the following form:

$$N_D = \frac{\alpha \cdot BCM}{C_{Ins} \cdot S_{Ins}}, \quad (8)$$

where α is the stimulated insulin production rate per cell, BCM is the beta cell mass, C_{Ins} is the homeostatic concentration of insulin in the body (i.e., fasting plasma insulin), and S_{Ins} is the insulin sensitivity index. The insulin sensitivity index is a measure of the rate of metabolism of glucose as a function of insulin concentration. However, measuring these variables is difficult in practice. As an alternative, the dimensionless number N_D was reformulated in terms of quantities that can be readily obtained in large-scale studies. This reformulated relationship, represented by ($\tilde{N}_D$), was developed in the following form:

$$\tilde{N}_D = \underbrace{\frac{SA_{Ins} \cdot \rho_B}{MW_{Glc}}}_{\text{Constants}} \cdot \underbrace{\frac{InsResp \cdot Wt \cdot 1000}{I1 \cdot \text{“SI Clamp”} \cdot G1 \cdot Wt}}_{\text{Specific to an individual}}, \quad (9)$$

where SA_{Ins} is the specific activity of insulin, ρ_B is the average density of the human body, Wt is the body weight of an individual, and MW_{Glc} is the molecular weight of glucose. $InsResp$ is the change in insulin concentration in response to an oral glucose tolerance test (OGTT) and is defined as:

$$InsResp = \frac{I2 - I1}{t}, \quad (10)$$

where t is the time between blood samples during the OGTT. $I1$ and $I2$ are the concentration of insulin in a fasted state (i.e., prior to the OGTT) and following the OGTT, respectively.

$InsResp$ represented the insulin production capacity for a population in response to a common stimulus: an OGTT. “SI Clamp” is an estimate of the sensitivity of the peripheral tissue to metabolize glucose in response to changes in insulin and is derived from a

hyperinsulemic glucose clamp. As insulin resistance plays an important role in the pathogenesis of diabetes^{14,13}, the hyperinsulemic clamp sets a high standard for assessing in vivo tissue sensitivity to insulin.¹⁵ Katz et al.²⁷ define the glucose clamp-derived index of insulin sensitivity as:

$$\text{SI Clamp} = \frac{M}{G \cdot dI \cdot Wt}, \quad (11)$$

where M is the steady state glucose infusion rate (mg/min), G is the steady state blood glucose concentration, dI is the difference between basal and steady state plasma insulin concentration, and Wt is the body weight. However, hyperinsulemic clamps are not easily applied in large-scale investigations due to the invasive nature and complexity of the protocol. Alternative measures have been proposed that are amenable to large-scale investigations and correlate highly with measurements of insulin sensitivity derived from hyperinsulemic clamps (e.g., HOMA³² and QUICKI²⁷). In this study, QUICKI was used as a surrogate estimate for “SI Clamp” (i.e., “SI Clamp” $\approx$ QUICKI). QUICKI was calculated from fasting plasma glucose ($G1$) and fasting plasma insulin ($I1$) using the formula reported by Katz et al.²⁷:

$$\text{QUICKI} = \frac{1}{\log(I1 \cdot G1)} \quad (12)$$

where $G1$ is the fasting glucose concentration. The terms in equation 9 were classified into two groups: variables that are constant across the patient population and variables that are unique to each individual. Subsequent analysis focused on the ratio of variables that vary across the population. The units associated with the variables in equation 9 that are assumed to vary among individuals are defined in Table 2.

3.2 Validation of the Dimensionless Number

Individuals with complete sets of data were identified in the third National Health and Nutrition Examination Survey (NHANES III)¹¹ and were stratified by disease state: normal ($n = 1197$), pre-diabetic ($n = 512$), known diabetic ($n = 142$), and unknown diabetic ($n = 234$) (see Supplemental Table S1 for patient data). The values for each of the variables reported were combined using equation 9 to estimate the dimensionless number, $\tilde{N}_D$, for each individual. A composite scatter plot for all of the different patient groups is shown in Figure 1. The color intensity shown in Figure 2 is linearly proportional to the probability density function for observing an individual with similar characteristics. Solid lines, each corresponding to a different patient group, enclose 50% of the population. The diagonal line corresponds to a value of $\tilde{N}_D$ equal to one. As the different patient groups clustered in different regions within the plots, the patient populations were also characterized along the diagonal. The diagonal corresponds to the direction that an individual may traverse if they were to increase in weight and maintain all other variables constant, i.e., the $\hat{W}t$ direction. However, all of the other variables do vary among individuals. The projection of an individual upon the $\hat{W}t$ axis was obtained using a two-dimensional rotation matrix:

$$\hat{W}t_i = \cos(45^\circ) \cdot \text{denominator of } \tilde{N}_{Di} + \sin(45^\circ) \cdot \text{numerator of } \tilde{N}_{Di} \quad (13)$$

where the index i corresponds to the values for a specific individual. In Figure 2, probability density functions are shown for the different patient groups projected onto the $\tilde{N}_D$ direction (panel A) and the $\hat{W}t$ direction (panel B). Note that $\tilde{N}_D$ direction and the $\hat{W}t$ directions are not orthogonal. Contour lines of constant $\tilde{N}_D$ are parallel to the diagonal shown in Figure Fig:s1. As $\tilde{N}_D$ is the ratio of the ordinate to the abscissa shown in Figure Fig:s1, an increase in $\tilde{N}_D$ can be achieved by a decrease in the abscissa while maintaining a constant ordinate or by an increase in the ordinate while maintaining a constant abscissa. The density function for $\tilde{N}_D$ in normals was centered around one while pre-diabetics, on average, exhibited a higher ratio than normals ($p < 0.001$). Suggesting that in normals there is a balance between insulin production and insulin-dependent glucose metabolism in individuals with normal glucose measurements. It is interesting to note that the normal group exhibits a slight bias towards lower values for $\tilde{N}_D$. In contrast, $\tilde{N}_D$ for known diabetics was almost a factor of 10 lower than normals ($p < 0.001$). Unknown diabetics, as a group, exhibited mixed characteristics between pre-diabetics and known diabetics. Along the $\hat{W}t$ axis, the mean value increased as the clinical characteristics changed from normal to pre-diabetic to diabetic. For comparison, values for the homeostasis model assessment (HOMA) were also calculated for each of the patients.

3.3 Comparison to Homeostasis Model Assessment

The Homeostasis Model Assessment (HOMA) is used to characterize the relative contributions of insulin resistance (HOMA-IR) and beta cell function (HOMA-B). The HOMA model is an empirical model developed to predict values for these metrics from fasting glucose and insulin measurements. In contrast to $\tilde{N}_D$, this empirical model does not account for differences in plasma volume among individuals.²⁵ A computer version of this model has been developed but the corresponding equations have not been described in the peer-reviewed literature.⁸ As an alternative, simple mathematical equations have been described that approximate the more detailed model.³⁰ HOMA-IR and HOMA-B can be calculated using the variables present in the NHANES III database from the following relationships:

$$\text{HOMA-IR} = \frac{I1P \times G1P/18}{22.5} \quad (14)$$

$$\text{HOMA-B} = \frac{20 \times I1P}{G1P/18 - 3.5} \quad (15)$$

A composite HOMA scatter plot for all of the different patient groups is shown in Figure 3. The color intensity shown in Figure 3 is linearly proportional to the probability density function for observing an individual with similar characteristics. Solid lines, each corresponding to a different patient group, enclose 50% of the population.

The HOMA metric provides individual estimates of insulin resistance and beta cell function based upon fasting measurements. In contrast, $\tilde{N}_D$ uses both fasting and dynamic measurements to estimate the insulin production capacity and insulin-dependent glucose metabolism. Theoretically, the HOMA and $\tilde{N}_D$ metrics should provide similar and independent estimates of these important components of glucose homeostasis. Plots of insulin resistance (subplot A) and beta cell function (subplot B) estimated from HOMA and $\tilde{N}_D$ are shown in Figure 4. The denominator of $\tilde{N}_D$ (i.e., insulin-dependent glucose metabolism) shows strong positive correlation with HOMA-IR ($r = 0.964$). This is expected as both metrics are calculated from fasting plasma glucose and fasting plasma insulin values. In contrast, the numerator of $\tilde{N}_D$ (i.e., insulin production capacity) and HOMA-B show moderate positive correlation ($r = 0.534$), as observed previously²². However visual inspection of Figure 4A suggests that the variance in HOMA-B varies with the numerator of $\tilde{N}_D$ and raises doubt about the validity of a correlation coefficient. In summary, these results suggest that HOMA-B is not correlated with the increase in plasma insulin following an OGTT.

In Figure 5, probability density functions are shown for the different patient groups projected onto the HOMA-B axis (panel A) and the HOMA-IR axis direction (panel B). Note that the marginal distributions for HOMA-B and HOMA-IR are displayed differently compared to the marginal distributions of $\tilde{N}_D$ and Wt shown in Figure 2. The density function for HOMA-B in normals was similar to pre-diabetic individuals ($p = 0.28$), while slightly higher from unknown diabetic individuals ($p = 0.011$). HOMA-B for known diabetic individuals was lower than both normal ($p < 0.002$) and pre-diabetic ($p < 0.001$) individuals. However, the known diabetic population appears to exhibit a bimodal distribution. Along the HOMA-IR axis, the mean value increased as the clinical characteristics changed from normal to pre-diabetic to diabetic ($p < 0.001$ for each pairwise comparison). In comparison to the dimensionless number results, HOMA metrics do not show that there is an increase in beta cell function in the pre-diabetic state. Moreover, the drop in beta cell function in known diabetic patients, as predicted by HOMA-B, was not as severe as predicted by $\tilde{N}_D$.

Differences in the two-dimensional probability density functions (PDFs) were used to quantify the ability of these two metrics (i.e., HOMA versus $\tilde{N}_D$) to classify individuals into their correct patient groups. For each metric, a p -value of 0.5 was used in equation 7 to estimate the fraction of a population that can be misclassified as belonging to another population (see Table 3). For five out of the twelve possible pairwise comparisons, the $\tilde{N}_D$ metric performed better than the HOMA metric. The ability of the HOMA metric to classify patient groups correctly is not surprising as the HOMA-B and HOMA-IR metrics are calculated from the same two fasting plasma measurements. Abnormal fasting plasma glucose is one of the measurements that the ADA criteria use to assign an individual to a patient population. In contrast, $\tilde{N}_D$ is based upon plasma measurements during a fasting state, OGTT responses, and body weight. Uncorrelated variability in these measurements may increase the likelihood for misclassification.

4 Discussion

The current methods for clinically classifying patients are based largely upon measurements obtained by sampling from the blood plasma. The limitations of plasma measurements to estimate beta cell function and insulin action are well documented.¹⁹ Given these limitations, numerous indices have been developed to characterize glucose homeostasis.¹² The disposition index⁶ (i.e., the hyperbolic law of glucose tolerance³⁹) bears the most similarity with the $\tilde{N}_D$ metric and has been defined as the product of the insulin sensitivity index and the insulin response to glucose. Π_1 and Π_2 represent a dimensionless form of these indices and a dimensionless disposition index would be the product of the Π 's (i.e., $DI = \Pi_1 \cdot \Pi_2$). As currently implemented, the indices for insulin sensitivity and insulin response to glucose are dimensional and obtained by fitting the dynamic response in insulin and glucose following an intravenous glucose tolerance test to Bergman's Minimal Model.⁴ In contrast to $\tilde{N}_D$, a reduction in either the insulin sensitivity index or insulin response to glucose result in a reduction in the product. Moreover, the disposition index does not consider the size of the system (i.e., the volume of distribution) as a variable. Based upon how dimensionless numbers are used in engineering, the dimensional nature of these indices limits their utility in translating information among systems. From a practical standpoint, understanding the relative influence of ethnic, gender, genetic, and environmental influences on glucose homeostasis is limited in a dimensional context. A dimensionless disposition index would help address some of these influences. However, values for all of the variables required to calculate a dimensionless disposition index are not typically measured in practice. In this paper, a dimensionless number is derived using the available information and validated to provide the foundation for understanding those relative influences.

In contrast to the correlative metrics commonly used in the field, the dimensionless number $\tilde{N}_D$ provides a method for distinguishing between different patient phenotypes based upon an understanding of the physiology underlying glucose homeostasis. It was postulated that glucose homeostasis is the net result of a balance between the ability of an individual to produce insulin and an individual's ability to metabolize glucose in response to insulin. Alterations in this balance result in precipitating the clinical symptoms of diabetes. Using this mechanistic basis, the dimensionless number $\tilde{N}_D$ facilitates physiological comparisons among individuals through dynamic scaling¹⁶, i.e., dynamic systems that exhibit a similar value are expected to behave similarly. As shown in Figure 2, normals exhibit a value of $\tilde{N}_D$ centered around 1. Pre-diabetics exhibited an increase in $\tilde{N}_D$ while clinical presentation of diabetes is characterized by a reduction in $\tilde{N}_D$. An increase in $\tilde{N}_D$ corresponds to a decrease in insulin-dependent glucose metabolism relative to what one might expect given an individual's insulin production capacity. A reduction in $\tilde{N}_D$ is consistent with a reduction in insulin production capacity relative to what one might expect given an individual's body weight and insulin-dependent glucose metabolism. Given a maximum level of insulin production per beta cell, a reduction in insulin production capacity would correspond to a reduction in an individual's beta cell mass. A reduction in beta cell mass has been observed in type 2 diabetics.¹⁰ Recently identified genetic loci that confer increased risk for type 2 diabetes are also associated with beta cell function.³⁶

It is anticipated that $\tilde{N}_D$ can be helpful to rationalize treatment options and identify high-risk sub-populations. This is illustrated by considering individuals with particular characteristics indicated by the numbers superimposed on Figure 6. Normal patient groups may not all have the same risk profiles (consider individuals clustered around point 1 versus point 2 in the panel A in figure 6). Normal individuals in group 1 exhibit low values for $\tilde{N}_D$. A subsequent increase in weight (red arrow), with other metrics remaining constant, for individuals in this subgroup of normals would suggest that they have a higher probability of becoming diabetic. In contrast, normal individuals with higher values for $\tilde{N}_D$ (point 2) could increase their weight by a similar amount (dotted arrow) and maintain glucose homeostasis. Similarly, consider the trajectories for disease progression for two different pre-diabetic groups (compare individuals around point 3 versus point 4 in panel B in Figure 6). Patients clustered around point 4 already have a low $\tilde{N}_D$ so increases in weight (i.e., traversal in the positive $\tilde{W}_t$ direction), with other metrics remaining constant, would suggest that they have a higher probability of becoming diabetic. In contrast, a reduction in $\tilde{N}_D$ would be required for individuals around point 3 to exhibit the same probability for become diabetic. These results suggest that weight gain may or may not be a good predictor of developing type 2 diabetes depending on the distribution of individuals enrolled in a particular study. However, the individual risk for developing type 2 diabetes upon weight gain may be very different. A recent study⁹ also supports different risk profiles for these patient clusters as individuals with an acute insulin response below the population mean exhibit an increased risk for developing type 2 diabetes.

Clinical research inevitably incorporates some level of bias as the patients that are studied have decided to visit a clinician and have agreed to enroll in a study. The NHANES III database provides a glimpse of a population typically unstudied: the unknown diabetic. For whatever reason, a clinician has never told patients in the unknown diabetic group that they have diabetes. In comparison to the known diabetic group, the unknown diabetic population exhibits higher insulin production capacity for the same body weight, is slightly younger (59.7 years versus 60.9 years, $p = 0.24$), and has lower levels of glycosylated hemoglobin (HbA1c) (6.70% versus 8.36%, $p < 0.0001$). The difference in HbA1c suggests that the unknown diabetic group exhibits better long-term control of plasma glucose. Duration of the diabetic symptoms may explain why these groups exhibit different capacities to produce insulin. Individuals classified as unknown diabetics may become known diabetic in time. However, the cross-sectional nature of the NHANES study is unable to address that question. Looking forward, $\tilde{N}_D$ can be incorporated readily into other large-scale studies as it is calculated from commonly used clinical tests (e.g., an OGTT with plasma insulin measurements). Ultimately, the trends identified using these common clinical tests to estimate insulin-dependent glucose metabolism should be confirmed using more direct test, such as the euglycemic hyperinsulinemic clamp.

In addition, treatment options may be rationalized using $\tilde{N}_D$ applied to different diabetic patient groups. Patients with a high $\tilde{N}_D$ may be successfully managed through weight loss. However, a combination of weight loss and a disease modifying therapy to increase $\tilde{N}_D$ may be required for patients with a low $\tilde{N}_D$ to revert to a normal phenotype. The dynamic trajectory that patients follows upon treatment (i.e., weight loss alone or in combination with drug treatment) would be important clinical evidence supporting restoration of glucose

homeostasis. In engineering, dimensionless numbers provide an important role in analyzing systems that cannot be easily studied at full scale. One might deduce that animal models that exhibit the same dynamic trajectory in $\tilde{N}_D$ as the clinical population provide the best representation of the human disease. Moreover, realistic models that accurately reflect the disease pathophysiology would be most appropriate for testing new drugs.

Individuals identified in the NHANES III database exclude patients likely to fall within a type 1 diabetes cohort due to constraints on oral glucose tolerance testing (i.e., age greater than 40 and not taking insulin). However, the qualitative analysis afforded by $\tilde{N}_D$ is relevant for the study of type 1 diabetes. A recent re-analysis of a series of landmark studies suggests that precipitation of the clinical symptoms of type 1 diabetes is the result of a balance between beta cell mass and body weight.²⁸ The beta cell mass required to maintain glucose homeostasis is proportional to body weight. In terms of the variables presented here, a reduction in beta cell mass for a constant weight corresponds to traversing in the negative $\tilde{N}_D$ direction. As weight increases, the reduction in $\tilde{N}_D$ necessary for clinical presentation decreases. A similar behavior is observed in the NHANES III data as shown in the panel A in Figure 6.

5 Conclusion

Detailed mechanistic models have been created that represent salient features of human physiology relevant to the pathophysiology of diabetes. However, application of such complicated models to provide feedback to individuals is prohibitive. As an alternative, a relationship was created from first principles to provide an expectation of how individuals should behave through dynamic scaling of glucose homeostasis. A reduction in insulin-dependent glucose metabolism and a reduction in insulin production capacity are typically associated with type 2 and type 1 diabetes, respectively. Dimensional analysis demonstrated that insulin-dependent glucose metabolism and insulin production are balanced in normals. Patients with pre-diabetic traits exhibit either a reduced insulin-dependent glucose metabolism or increased insulin production capacity given their body weight. It might be expected that progression to frank diabetes would correspond to further reduction in insulin-dependent glucose metabolism. However, the predominant feature of the population with diabetes was a marked reduction in insulin production capacity. Differences between the expected behaviors and new data provide the engine for scientific progress.³⁴

The dimensionless relationship developed here may also help improve treatment of diabetes. In particular, this dimensionless number may be used to monitor basic physiological variables responsible for glucose homeostasis in the clinic. Deducing the potential impact of $\tilde{N}_D$ from how dimensionless numbers are used in engineering, similarity in dynamic trajectories within this dimensionless “space” could provide a criterion for selecting relevant animal models for diabetes. Furthermore, genetic studies could stratify patient populations into different subpopulations based upon their dynamic trajectories. Stratification could improve the power associated with these studies and aid in identifying multivariate contributions. The validation of this dimensionless number is intended to connect the rich history associated with dimensionless numbers in engineering with one of the major health challenges of our time: type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations

HOMA	Homeostasis Model Assessment
NHANES III	Third National Health and Nutrition Examination Survey
OGTT	oral glucose tolerance test
PDF	probability density function

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Figure 1.

A composite image of the dimensionless number $\tilde{N}_D$ plotted for every individual, shaded by prevalence within the patient group, identified in the NHANES III database. Results are stratified by patient category (Normals - black, Pre-diabetic - blue, Unknown diabetic - gold, and Known diabetic - red). The solid diagonal line indicates where $\tilde{N}_D$ is equal to 1. Each individual is represented by a circle. The intensity of the filled color is related to the two-dimensional density of individuals within a category. The x-axis corresponds to the estimate of the denominator of $N_D(C_{\text{Ins}}, S_{\text{Ins}})$, which is related to insulin-dependent glucose metabolism, and the y-axis corresponds to the estimate of the numerator of $N_D(\alpha \cdot \text{BCM})$, which is related to insulin production. Curved lines, corresponding to each patient category, enclose 50% of the population. The arrow indicate directions of increasing $\tilde{N}_D$ and $\hat{W}_t$, respectively.

■ Normal; ■ Pre-diabetic; ■ Unknown diabetic; ■ Known diabetic

Figure 2.

The distribution in values for $\tilde{N}_D$ (A) and distance from the origin along $\hat{W}t$ direction (B) for each of the different patient groups (Normals - black, Pre-diabetic - blue, Unknown diabetic - gold, and Known diabetic - red). The one-dimensional density distributions were obtained by kernel density estimation. The dotted line in the panel A highlights a value of N_D equal to one.

Figure 3.

A composite image of the Homeostasis Model Assessment plotted for every individual, shaded by prevalence within the patient group, identified in the NHANES III database. Results are stratified by patient category (Normals - black, Pre-diabetic - blue, Unknown diabetic - gold, Known diabetic - red). Each individual is represented by a circle. The intensity of the filled color is related to the two-dimensional density of individuals within a category. The x-axis corresponds to the estimate of the insulin resistance, HOMA-IR, and the y-axis corresponds to the estimate of the insulin production, HOMA-B. Curved lines, corresponding to each patient category, enclose 50% of the population.

Figure 4.

The metrics for insulin production (A) and insulin-dependent glucose metabolism (B) as estimated by $\tilde{N}_D$ (x-axes) and HOMA (y-axes). HOMA-B and the numerator of $\tilde{N}_D$ (i.e., $\alpha \cdot \text{BCM}$) are moderately positively correlated ($r = 0.534$). HOMA-IR and the denominator of $\tilde{N}_D$ (i.e., $C_{\text{Ins}} \cdot S_{\text{Ins}}$) exhibit strong positive correlation ($r = 0.964$).

Figure 5.

The distribution in values for HOMA-B (A) and HOMA-IR (B) for each of the different patient groups (Normals - black, Pre-diabetic - blue, Unknown diabetic - gold, and Known diabetics - red). The one-dimensional distributions are represented by probability density functions that were obtained by kernel density estimation.

Figure 6.

Shaded scatter plots of the dimensionless number $\tilde{N}_D$ for each of the individuals identified in the NHANES III database. (A) Normals (blue) are shown against individuals diagnosed with diabetes (known diabetics - red). The numbered red arrows indicate the direction that patients traverse if they were to gain weight and maintain all other variables constant. (B) Individuals with pre-diabetic symptoms (black) are shown against known diabetics (red). The numbered red arrows on panel B indicate the direction for decreasing values of $\tilde{N}_D$ (arrow labeled with a 3) and increasing values of weight (Wt) (arrow labeled with a 4). The solid diagonal line in each subplot indicates where $\tilde{N}_D$ is equal to 1. Each individual is represented by a circle. The intensity of the filled color is related to the two-dimensional density of individuals within a category. The x-axis corresponds to the insulin-dependent glucose metabolism (i.e., $C_{Ins} \cdot S_{Ins}$) and the y-axis corresponds to the insulin production (i.e., $\alpha \cdot BCM$).

Table 1

A subset of biological variables that represent important characteristics of glucose homeostasis.

Variable	Definition	Fundamental Units
S_{Ins}	Insulin sensitivity	$\frac{\text{mole}}{\text{time}} \cdot \frac{\text{length}^3}{\text{mole}}$
C_{Ins}	Insulin concentration	$\frac{\text{mole}}{\text{length}^3}$
α	Stimulated insulin production per beta cell	$\frac{\text{mole}}{\text{time} \cdot \text{mass}}$
BCM	Beta cell mass	mass
k_d	Rate constant associated with insulin consumption	$\frac{1}{\text{time}}$
V	Volume equivalent of the human body	length^3

Table 2

Variables used in calculating $\tilde{N}_D$ and corresponding variables defined in the NHANES III.

$\tilde{N}_D$ Variable	NHANES Variable	Definition	Units
–	HAD1	Health care provider identified diabetes	–
G1	G1P	Fasting plasma glucose	mg dL ⁻¹
t	G1PTIM1	Minutes between drink and second draw	min
I1	I1P	Serum insulin at first draw	μU mL ⁻¹
I2	I2P	Serum insulin at second draw	μU mL ⁻¹
Wt	BMPWT	Body mass	kg
QUICKI	–	Estimate of insulin sensitivity ²⁷	$\frac{mg}{min} \cdot \frac{mL}{\mu U} \cdot \frac{dL}{mg} \cdot \frac{1}{kg}$

A comparison of classification error between the HOMA metric (top) and the $\tilde{N}_D$ metric (bottom). A classification error is defined as the fraction of each patient group that can be misclassified into another patient group.

Table 3

HOMA metric				
Real Group				
Misclassified Group	Normal	Pre-diabetic	Unknown Diabetic	Known Diabetic
	–	0.474	0.308	0.125
	Pre-diabetic	0.198	–	0.461
	Unknown Diabetic	0.071	0.127	–
Known Diabetic	0.027	0.055	0.287	–
$\tilde{N}_D$ metric				
Real Group				
Misclassified Group	Normal	Pre-diabetic	Unknown Diabetic	Known Diabetic
	–	0.251	0.216	0.233
	Pre-diabetic	0.368	–	0.494
	Unknown Diabetic	0.295	0.189	–
Known Diabetic	0.119	0.119	0.284	–