Hyperglycemia in type 2 diabetes: physiological and clinical implications of a brain centered model

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Abstract:

The hyperglycemia of type 2 diabetes has been classically believed to be a result of insulin resistance and relative insulin deficiency. However, the unexpected outcomes of insulin receptor knockout and insulin suppression experiments and the unexplained patterns in clinical data have exposed the limitations of the peripheral regulation models. Absence of fasting hyperglycemia by insulin receptor knockouts or insulin suppression, evidence for hyperinsulinemia preceding insulin resistance, the perplexing hyperinsulinemic normoglycemic state, reduced glucose transport to the brain preceding hyperglycemia, absent or poor correlation between fasting glucose and insulin, very strong positive correlation between indices of insulin resistance and β cell function in population data are some of the anomalous findings which glucose homeostasis models have not addressed so far. On the other hand the increasing evidence of central neuronal mechanisms of glucose regulation necessitates incorporation of brain glucose regulation in the models. Although models considering brain glucose regulation have been suggested, their multiple physiological and clinical implications have not been thoroughly examined. Based on updated evidence, we propose a refined model of glucose regulation that considers brain glucose levels as the ultimate target of homeostasis and combines central and peripheral mechanisms of regulation. In this model, considering reduced rate of blood to brain transmission of glucose and insulin as primary pathology explains most of the patterns including apparent anomalies with or without including insulin resistance. A brain centered model accounts for the limited and inconsistent success of glucose normalization in effectively reducing diabetic complications and mortality. A serious attempt to reevaluate alternative models is required since the brain centered model implies radical changes in the target and the course of diabetes treatment.

Key words: Glucose homeostasis, hyperglycemia, type 2 diabetes, steady state

Presently, any metabolic disorder with consistent raised plasma glucose and insulin resistance, which cannot be categorized into either type 1 diabetes or gestational diabetes is defined as type 2 diabetesmellitus (T2DM) (DeFronzo et al., 2015). It is the most common form of diabetes, accounting for almost 90% of all cases.The currently perceived cause of hyperglycemia in T2DM is insulin resistance followed by failure of compensatory insulin response. Historically the role of brain in glucose homeostasis was revealed by experiments in which damage to the fourth cerebral ventricle was shown to impair homeostatic control (Bernard, 1859). However, at a later stage, pancreatic extracts were shown to lower glucose and eventually insulin was identified as the active principle (Banting et al., 1922). It is necessary to note that the differentiation of type 1 and type 2 diabetes was not made at that time. The success of insulin was so spectacular that all other mechanisms of glucose regulation were almost forgotten for about a century (Lundqvist et al., 2019). The distinction between type 1 and type 2 diabetes was to become clear half a century later and it was realized that unlike in type 1, insulin deficiency was not the primary cause of hyperglycemia in type 2 diabetes. However, by this time the thinking in the field was so much insulin centered that the inability of normal or increased levels of insulin to regulate plasma glucose was termed insulin resistance, without carefully evaluating alternative hypotheses.

Further,the insulin resistance hypothesis is criticized for having a circular logic which makes it un-falsifiable (Diwekar-Joshi&Watve, 2020). Insulin resistance is said to be responsible for the inability of normal or raised levels of insulin to regulate glucose. However, insulin resistance itself is measured by the inability of insulin to regulate glucose. There is no independent measure of insulin resistance that can be used to test the causal role of insulin resistance. Impairment of insulin signaling in experiments using (i) tissue specific insulin receptor knockouts (Blüher et al., 2002; Kadowaki, 2000) (ii) insulin degrading enzyme knockouts (Costes & Butler, 2014; Maianti et al., 2014) (iii) pharmaceutical insulin suppression by diazoxide and octreotide (Giustina et al., 1991; Lamberts & Hofland, 2019; Leahy et al., 1994; Matsuda et al., 2002)(iv) insulin gene suppression by RNAi (Mehran et al., 2012b) (v) alteration in insulin gene dosage (Templeman et al., 2015) does not consistently alter fasting glucose although it alters the post meal glucose curve. In epidemiological data, fasting insulin and fasting glucose are poorly correlated while post meal insulin and glucose are strongly correlated, unlike what would be expected by any of the models. With

converging multiple lines of evidence Diwekar-Joshi and Watve (2020) raised doubts on whether insulin resistance and failure of compensatory hyperinsulinemia is a necessary and sufficient explanation of fasting hyperglycemia.

Many mathematical models have been constructed based on the assumption of insulin resistance. A common set of assumptions is shared by most of the models that fasting glucose is the steady state achieved by a balance between glucose uptake by tissues and glucose production by liver. One of the foundational assumptions is that both the above processes are regulated by insulin signaling in the steady state (Matthews et al., 1985). Therefore insulin signaling has been central to these models. Since recent research has exposed the inadequacies of this model (Diwekar-Joshi & Watve, 2020) there is a need to hunt for better alternative models.

An alternative to the classical model which assumes brain glucose level as the target of homeostasis has been suggested and mathematical models incorporating this concept have been constructed (Gaohua & Kimura, 2009; Watve, 2013). These models have not been explored sufficiently towards a comparative evaluation with peripheral models with respect to their predictions and their physiological as well as clinical implications. Here we refine the brain centered model further incorporating recent evidence, evaluate its performance and explore the physiological and clinical implications.

<u>What a glucose homeostasis model needs to explain</u>:

Most models of glucose homeostasis have a limited goal of explaining altered fasting steady state glucose level and the alterations in the glucose curve in the pre-diabetic and diabetic state. However, now we have a large number of experimental results that are potentially anomalous. A model prediction matrix, in which each model is tested for matching its prediction with multiple known empirical patterns, is an appropriate and robust approach to compare alternative models. Such an approach has been used to test alternative hypothesis in a number of other contexts (Thakar et al 2003, Diwekar and Watve 2016, Vibishan and Watve 2020, Shinde et al 2021) and it can be the right approach to test alternative models of glucose homeostasis in T2DM. A model of choice would be one which can predict all or most of the known physiological patterns in type 2 diabetes so that no or minimal anomalies

are left. We take a few steps towards a model prediction matrix, although a lot more exploration of many other models is required before constructing such a matrix.

Following is the list of known empirical patterns that a model needs to be compatible with.

1. The model should allow stable steady state glucose on fasting: Fasting glucose is assumed to be a steady state with adequate evidence (Lerner & Porte, 1972; Matthews et al., 1985; R. C. Turner et al., 1979). Achieving a steady state is one of the primary objectives of every homeostasis model. Many of the key concepts of classical models are also based on achieving a steady state in the fasting condition (Matthews et al., 1985; R. C. Turner et al., 1979).
2. The model should also allow stable steady state insulin on fasting. Normally this is not a problem for any model, however many models have a problem in explaining the altered steady state insulin level in a prediabetic state as explained below.
3. Hyperinsulinemic normoglycemic condition in the prediabetic state: A prediabetic state is often accompanied by high level of fasting insulin (FI) but normal fasting glucose (FG) in the plasma. This is not easy to achieve in a model. The classical qualitative explanation of this state is that it is a state of insulin resistance with compensatory rise in FI such that FG remains normal. For this to happen, there is a need to estimate the level of insulin resistance and regulate insulin secretion accordingly. It is possible to hypothesize a mechanism of sensing insulin resistance and conveying this information to the pancreas. Such a mechanism can be glucose dependent or glucose independent. Currently no glucose independent mechanism of accurately assessing the insulin resistance and conveying it to β cells is known. A common assumption is that insulin resistance reduces glucose uptake thereby increasing FG. The rise in FG stimulates insulin production and the rise in insulin levels normalizes glucose again. However, this mechanism fails to achieve a steady state hyperinsulinemic normoglycemic condition (Diwekar-Joshi & Watve, 2020). Plasma insulin has a short half life and after glucose levels are normalized, it is unlikely to stay at a higher level unless there is a glucose independent trigger for insulin secretion. Explaining a hyperinsulinemic, normoglycemic steady state is a tricky challenge that any model needs to meet.

4. Hyperinsulinemia precedes insulin resistance and T2DM: Although hyperinsulinemia is believed to be a compensatory response to insulin resistance, a number of studies show that hyperinsulinemia precedes obesity and insulin resistance (Corkey &Shirihai, 2012; Mehran et al., 2012a; Pories & Dohm, 2020; Shanik et al., 2008; Weyer et al., 2000; Wiebe et al., 2021). This raises two independent questions. One is how and why hyperinsulinemia precedes insulin resistance. The second,more perplexing question is that if hyperinsulinemia is not a compensatory response to insulin resistance, the failure of compensation explanation becomes redundant. This needs to be replaced by a more coherent explanation of hyperglycemia.
5. The model should explain the following features of post meal glucose curve and its alterations in prediabetic and diabetic states, which cumulatively are called impaired glucose tolerance curve.
   - Increased height of peaks
   - Delayed return to normal
   - Increase in the time difference in glucose and insulin peaks in the diabetic state.
6. The normal fasting glucose, impaired glucose tolerance (NFG-IGT) state: It is common to find that in a prediabetic state the glucose tolerance curve is altered with normal level of fasting glucose. A good model needs to explain the NFG-IGT phenomenon.
7. Stress hyperglycemia: Why and how stress causes hyperglycemia only in some individuals (Dungan et al., 2009) needs to be explained by a model with realistic and testable assumption.
8. Hyperglycemia after intensive exercise: If in a fasting state FG is a resultant of the rate of liver glucose production and glucose disposal, exercise that increases glucose disposal should decrease FG. However, in some studies plasma glucose remains unchanged or is increased after exercise (Coggan, 1991; Marliss & Vranic, 2002). A model needs to incorporate this phenomenon.
9. An important challenge is to explain why insulin receptor knockouts specific to muscle, fat cell or liver results into normal fasting glucose but altered post glucose load curves. Similarly, insulin degrading enzyme knockouts do not alter FG. Also insulin suppression by agents such as octreotide or diazoxide fail to alter FG (Diwekar-Joshi & Watve, 2020). A model should explain this observation. Diwekar-

Joshi and Watve (2020) further differentiated between the consequential steady state (CSS) and targeted steady state (TSS) models and demonstrated that the results of the insulin receptor knock out and insulin suppression experiments can be explained by a TSS but not by a CSS model. In effect, to be able to account for these results a model needs to be a TSS model.

10. Reduced glucose transport to brain, particularly in obese or prediabetic individuals: It is known over a long time that in type 2 diabetes the rate of glucose transport from blood to brain is slowed down substantially (Gjedde & Crone, 1981). In rodent models, the glut-1 expression in brain capillaries is shown to be reduced (Cornford et al., 1995; Matthews et al., 1985; Pardridge et al., 1990). This has been viewed as a response to hyperglycemia. However, Hwang et al (2017) show that subnormal transport is evident in obese and presumably prediabetic state, even before hyperglycemia appears. A model needs to account for this pattern as a causal or consequential phenomenon.
11. The T2DM specific islet amyloid deposition which often accompanies islet deterioration: Islet amyloid deposition is frequently associated with type 2 diabetes but not observed in type 1. The causes of islet amyloid deposition should be compatible with the glucose homeostasis model (Höppener et al., 1999; Porte & Kahn, 1989; Watve, 2014).
12. The pattern of B cell deterioration: The deterioration of β cells appears to follow a peculiar pattern in T2DM, in which a substantial proportion of β cells survive lifelong (Bacha et al., 2013; Butler et al., 2003; Clark et al., 2001; Porte & Kahn, 2001; Watve, 2014). If dysfunction and damage to the β cell population is assumed to be an essential prerequisite of hyperglycemia in a model, the models need to account for the peculiar population dynamics of β cells.
13. SGLT2 inhibitors increase liver glucose production as well as ketogenesis: Over the last decade SGLT2 inhibitors, which allow greater clearance of glucose through urine, have offered a novel means of combating hyperglycemia. Lowering of plasma glucose by SGLT2 inhibitors is accompanied by increased liver glucose production as well as increased ketogenesis (Limenta et al., 2019; Mistry & Eschler, 2021; Op den Kamp et al., 2021; Pfützner et al., 2017). A glucose homeostasis model needs to account for this phenomenon.

14. The Somogyi phenomenon i.e., hyperglycemia following infusion of insulin is seen in at least some cases of T2DM but not in healthy individuals. This can happen without being overtly hypoglycemic (Campbell, 1976; Reyhanoglu & Rehman, 2021). This phenomenon needs to be incorporated by a good model of glucose homoeostasis.
15. In cases of brain injury hyperglycemia is common (Shi et al., 2016). In bacterial meningitis hyperglycemia is often observed accompanied by low CSF glucose level (Krishnan et al., 2016; Schut et al., 2009). A model should be able to account for these phenomena.
16. In population data one sees good correlation between post meal glucose and insulin but poor correlation between FG and FI (Diwekar-Joshi & Watve, 2020). This population pattern should be explained by a comprehensive model.
17. Although FG and FI are poorly correlated in prediabetic state, HOMA-β and HOMA-IR have strong positive correlation in population data (Diwekar-Joshi & Watve, 2020). A model should predict such a pattern in a population.
18. Failure of glucose normalization to reduce the frequency of complications and mortality: Unlike T1DM, in T2DM tight regulation of plasma glucose has failed to show reduction in mortality consistently across multiple large scale clinical trials (Diabetes Prevention Program Research Group, 2015; Ferrannini & DeFronzo, 2015; King et al., 1999; Klein, 2010; Lee et al., 2021; Schwartz & Meinert, 2004; R. Turner et al., 1998; The NICE-SUGAR Study Investigators, 2009, UK Prospective Diabetes Study (UKPDS) Group, 1998). If hyperglycemia is the primary pathology of type 2 diabetes, preventing or correcting it should have reduced the frequency of complications and mortality considerably.
19. Reversal of hyperglycemia by FGF 21 in all models of rodent diabetes: Independent of the cause of hyperglycemia, a single injection of FGF 21 was able to achieve long term normalization of plasma glucose (Laeger et al., 2017). This is a potential anomaly that a model needs to resolve.

While most models intend to explain 1, 2 and 5 of the above, they either fail to explain or do not address the others. Our expectation from a satisfactory model is that it should inherently predict these outcomes or should be compatible with them. If an additional explanation that does not contradict the model, accounts for the phenomenon, the model is compatible. Compatibility with empirical findings cannot be taken as a proof or validation of

the model, but if a model directly contradicts one or more of the empirical findings, it becomes serious grounds for rejecting the model. Later when we describe model results, we will use the numbers in the above list in square brackets to indicate that the model accounted for this pattern.

Peripheral models of glucose homoeostasis:

There is a rich history of development of mathematical models of glucose homeostasis and the origin and progression of type 1 and type 2 diabetes (reviewed by Ajmera et al., 2013; Mari et al., 2020). The focus of the field is so much on peripheral mechanism that the review by Mari et al (2020) does not even cite the models incorporating the role of brain. Ajmera et al (2013) briefly mention the Gouhua et al (2009) model but do not elaborate on its potential implications. A class of models attempts to capture glucose homeostasis at the systems levels whereas other models look at individual components such as insulin dependent glucose uptake, liver glucose production, β cell dysfunction, glucose stimulated insulin secretion and incretin effects at greater details. Nevertheless, these models together have not accounted for many of the patterns listed above. The central assumption of these models is more or less invariant and revolves around insulin resistance and the failure of insulin response to adequately compensate for it (Mari et al., 2020). Diwekar-Joshi and Watve (2020) claimed that any model with this set of assumptions is not compatible with empirical patterns 3,4,6,9, 16 and 17 of the above. Whether any variation of these models can do so has not been adequately explored. Furthermore, all the peripheral regulation models are CSS models in that the fasting steady state is a consequence of the rate of liver glucose production and a concentration dependent rate of glucose uptake. In these models a change in either or both the rates inevitably alters the steady state. This contrasts the TSS models in which alteration in these rates alters the time required to reach a steady state but does not alter the steady state glucose level (Diwekar-Joshi & Watve, 2020). An attempt to develop a TSS model with only peripheral mechanisms has not been made to the best of our knowledge.

We do not intend to review glucose homeostasis models here. However, we observe from published reviews of glucose homeostasis models (Ajmera et al., 2013; Mari et al., 2020)that most models do not address the apparently anomalous empirical findings particularly 3, 4,

6, 9, 10, 11, 12 ,13 and 15-18 among the ones listed above. A detailed exploration in to whether some variations of these models can address the apparently anomalous patterns is beyond the scope of this paper but we remain open to this possibility.

Brain centered models of glucose homeostasis**:**

It is quite well known that a number of neuronal mechanisms in the brain are involved in energy homeostasis. Nevertheless, for some reason, they do not occupy a central stage in the mainstream thinking in T2DM and glucose regulation models. A number of recent publications highlight the role of brain in different ways (Lam, 2005; Osundiji et al., 2012; Perrin et al., 2004; Watve, 2013, Lundqvist et al 2019). Peters (2004), Gaohua and Kimura (2009) and Watve (2013) proposed that the primary target of glucose homeostasis is to regulate glucose levels in the brain. Plasma glucose levels are only a means to achieve required supply of glucose mainly to the brain. Since transport of glucose to the brain is more restricted, when adequate supply of glucose to the brain in ensured, it is likely that the supply to other organs already gets ensured.

In the Gaohua and Kimura (2009) as well as in the Watve (2013) model the rate of glucose transport across the BBB is assumed to be an adaptation to hyperglycemia. The finding that glucose transport is reduced to an intermediate level in obese and prediabetic individuals (Büsing et al., 2013; Hwang et al., 2017) suggests that the deficiency in transport precedes hyperglycemia rather than following it. Therefore, it is more likely to be causal than consequential. Glucose deficiency in the brain is known to induce liver glucose production and suppresses insulin release through autonomic control (Boland et al., 2017). Sympathetic tone has also been shown to be higher in T2DM (Thackeray et al., 2012). Therefore glucose deficiency in the brain owing to altered vascular function is likely to be primary which results in altered plasma glucose dynamics mediated by autonomic inputs. Our model incorporates this possibility.

Impaired vascular function is known to be central to diabetic complications. The classical thinking has been that hyperglycemia causes the types of vasculopathies typical of T2DM. However, it has not been ruled out that vasculopathies are not primary. There is considerable evidence that microvascular alterations precede T2DM and are good predictors of it (Muris et al., 2012; Nguyen et al., 2007; Stehouwer, 2018; Zaleska-Żmijewska

et al., 2017). Sedentary life style and deficiency of many specific types of physical activities and behaviors alter the expression of growth factors and endocrine mechanisms involved in angiogenesis. It has been demonstrated repeatedly that many growth factors and angiogenic factors are responsive to behaviors, physical activity and exercise (Aloe et al., 1994; Cao et al., 2010; Chodari et al., 2016; Lakshmanan, 1986; Nexø et al., 1984; NEXØ et al., 1981; Tirassa et al., 2003). Deficiency of these behaviors is likely to lead to a primary deficiency of angiogenic mechanisms(Watve, 2013). We consider the possibility that altered vascular function in the brain is the primary reason why glucose transport from blood to brain is reduced. This creates chronic glucose deficiency in the brain to which the brain reacts by influencing multiple mechanisms of glucose regulation. The predominant mechanism is autonomic signaling. It is well known that sympathetic and parasympathetic tones are altered in T2DM (Thackeray et al., 2012). We consider the possibility that altered autonomic signaling is causal rather than consequential to diabetes, based on studies showing that changes in autonomic function precede T2DM (Carnethon et al., 2003).

The brain glucose uptake is insulin independent (Gray et al., 2014; Hasselbalch et al., 1999). Nevertheless insulin has many other functions in the brain and insulin signaling is known to be important in memory, cognition, decision making and behavior (Kerns 2001, Shemesh et al., 2012; Strachan, 2003). Brain is rich in insulin receptors and activation of certain cognitive functions in the brain is a likely cause of increased brain glucose utilization by insulin stimulation (Bingham et al., 2002; Rebelos et al., 2021). We assume therefore that brain has a fundamental requirement for insulin, independent of glucose metabolism and therefore mechanisms to ensure the required insulin levels in the brain are as much critical as ensuring minimum brain-glucose level. This is also ensured by autonomic mechanisms. Autonomic inputs are known to regulate β cell population and as well as insulin release from β cells (Thorens, 2015). Therefore, our model also incorporates brain control over insulin production.

Ensuring minimum supply of glucose as well as insulin to the brain is crucial during fasting when the plasma levels are low. The post meal levels of glucose and insulin in the plasma are much higher and at this time, the brain need not actively regulate the plasma levels of both. This can be taken care of by the peripheral mechanisms.

<u>Objectives of the model</u>**:**

Our attempt is to construct a model whose predicted outcomes match with all or most of the observed phenomena listed above, qualitatively. We intend to construct a model in which different hypotheses for hyperglycemia can be used to make differential testable predictions. This approach can allow us to evaluate comparatively which causal factors individually or in combination can give us the set of predictions that match with the patterns listed above.

Out of the parameters required for the model, only some have empirical estimates available (table 1). In the absence of realistic estimates of all parameters, we do not intend to make a model making quantitative predictions. When a sufficiently large number of parameters can be optimized, it is not difficult to fit the data quantitatively. Therefore we prefer qualitative predictions over quantitative ones. We test whether the model is able to predict the pattern observed empirically under some set of parameters. The ability to predict a given pattern is not a proof of the validity of the model, but the inability to predict an observed phenomenon at any set of parameters in a realistic range is a strong reason to call the model either inadequate or wrong. If an additional consideration compatible with the model is able to explain a pattern not explained by the main model, the model can be called inadequate but not falsified. However, if the model outcome directly contradicts a consistent and reproducible empirical finding, it can be considered falsifying evidence. We emphasize the need to evaluate our model in comparison with classical models on these lines.

<u>Assumptions of the model</u>**:**

A unique assumption of our model based on the analysis by Diwekar-Joshi and Watve (2020) is that the mechanism of regulation of glucose and insulin is different in the steady state and post meal state. In the steady state the central mechanisms are more important whereas in post meal state mainly the peripheral mechanisms are at work. Insulin induced glucose uptake and insulin dependent inhibition of liver glucose production happen only above a threshold glucose and insulin level respectively. The presence of such thresholds and their context dependent variability has been known for a long time (Chen et al., 1993; Henquin et al., 2006; Sorensen 1985). Below the threshold, other mechanisms regulate the levels (Sorensen 1985). We assume in the model that the thresholds are under neuro-endocrine control and fine-tuned by the brain. The thresholds found in isolated cell cultures are slightly

lower than the normal fasting blood sugar and it is difficult to estimate thresholds in vivo (Chen et al., 1993; Henquin et al., 2006, 2015). In presence of autonomic signals, we assume the thresholds to be above the steady state target levels. In conditions under which the fasting levels need to increase, we assume the thresholds to increase proportionately. This may happen with peripheral or central mechanisms. These assumptions about the threshold make the model a TSS model.

The steady state glucose is decided by a balance between basal level of liver glucose production which is regulated by neuronal mechanisms and insulin independent glucose uptake by tissues.The steady state insulin level is decided by basal rate of glucose independent insulin production, which is regulated by neuronal mechanisms against the insulin degradation rate. Glucose is transported from plasma to brain by facilitated diffusion proportionate to capillary surface area in the brain and glut-1 expression. Steady state brain glucose is determined by glucose transport to brain and utilization by brain tissue. Brain needs a target level of glucose and the brain ensures the minimum by directly regulating liver glucose production by neuronal mechanisms.

Insulin has cognitive and other functions in the brain (Begg & Woods, 2013; Kern et al., 2001; Rohner-Jeanrenaud & Jeanrenaud, 1983; Shemesh et al., 2012; M W J Strachan, 2005), for which the brain requires a target level of insulin, which it ensures by autonomic regulation of β cell number and basal insulin secretion independent of glucose. For ensuring the brain target level for insulin, a minimum plasma insulin level needs to be maintained. Maintenance of this level is assumed to be independent of glucose stimulated insulin secretion.

The rate of transport of glucose and insulin from blood to brain is not constant. Both are affected by the capillary density and blood flow. But they also depend upon specific transport mechanisms. Glucose is transported across the blood brain barrier mainly through the specific transporter glut-1. The expression of glut-1 in brain and other tissues is variable and dependent on multiple dietary, endocrine and growth factor related mechanisms (Boado et al., 1994; Ge et al., 2011; Liu et al., 2018; Schüler et al., 2018).Glucose transport from blood to brain is diminished in obesity and prediabetes (Hwang et al., 2017). Insulin transport to brain is also reduced in obesity (Begg, 2015). The ratio of CSF to plasma insulin is inversely proportionate to obesity and insulin resistance (Gray & Barrett, 2018). Moreover

381 inducing endothelial dysfunction and reducing glucose transport experimentally by
382 endothelial specific deletion of HIF 1 α resulted into hyperglycemia (Huang et al 2012).
383 Based on such multiple lines of evidence we incorporate the possibility of diminished
384 glucose and insulin transport to brain being the primary pathology of T2DM and
385 hyperglycemia only a consequence.

386 **The model**:

387 Since we assume that the steady state and post meal mechanisms of glucose regulations are
388 not identical, we model and analyze the two states in two phases of the model. The
389 variables and parameters used in the model and the range of parameter used are in table 1.

sr no	Variables and parameters	meaning	units	Value/range used in simulations
A. Input parameters				
1	K_1	Insulin independent glucose uptake maximum	mg/dL/min	20-50
2	K_{1m}	Half saturation constant for insulin independent glucose uptake	mg/dl	50
3	K_2	Maximum insulin induced suppression of *PG*, including glucose disposal and suppression of *L*.	per μU/mL	0.001 to 0.05
4	K_{2m}	Half saturation constant for insulin induced suppression of *PG*	μU/mL	15
5	K_5	Maximum glucose dependent insulin secretion	μU/mL/min	2-20
6	K_{5m}	Half saturation constant for glucose induced insulin secretion	mg/dL	50
7	K_8	Maximum rate of glucose transport to brain	Mg/dL/min	3 - 8
8	K_{8m}	Half saturation constant for glucose transport to brain	mg/dL	50-100
9	K_9	Maximum rate of Insulin transport	μU/mL/min	0.6 - 1

		to brain		
10	K_{9m}	Half saturation constant for insulin transport to brain	µU/mL	0.3-1
11	K_{10}	Brain glucose utilization rate	unitless	0.08 to 0.12
12	d_1	Insulin degradation rate	unitless	0.1 to 0.2
13	*BGt*	Target *BG*	mg/dL	25
14	*BIt*	Target *BI*	µU/mL	1-5
15	I_s	Insulin sensitivity as compared to normal which is assumed 1.	unitless	0-1
16	L_{max}	Maximum capacity of liver glucose production	Mg/dL/min	30
17	K_{4max}	Maximum capacity of glucose independent insulin secretion	µU/mL/min	10
B. Derived variables				
18	*L*	Rate of liver glucose production	mg/dL/min	Eq. 6 or iterative
19	K_4	Rate of glucose independent insulin secretion	µU/mL/min	Eq 7 and 8 or iterative
C. Outcome variables				
20	*PG*	Plasma glucose	Mg/dL	dynamic
21	*PI*	Plasma insulin	µU/mL	dynamic
22	$\underline{PG}$	Steady state plasma glucose	mg/dL	Eq. 5
23	$\underline{PI}$	Steady state plasma insulin	µU/mL	Eq. 7
24	*BG*	Brain glucose	mg/dL	dynamic
25	*BI*	Brain insulin concentration	µU/mL	dynamic
26	*PGT*	glucose threshold above which GSIS begins	mg/dL	5 to 10 mg/dL above $\underline{PG}$
27	*PIT*	Insulin threshold above which insulin induced glucose disposal begins	µU/mL	2-5 µU/mL above $\underline{PI}$

Table 1: all variables and parameters considered in the model.

A: Modeling steady state glucose:

As per the assumption, below a threshold *PI*, insulin induced glucose uptake and insulin induced inhibition of liver glucose production is negligible,

1. Plasma Glucose:

$$\frac{dPG}{dt} = \begin{cases} L - \frac{K_1 * PG}{K_{1m} + PG}, \ + Gt & (\underline{PI} < PIT) \\ L - \frac{K_1 * PG}{K_{1m} + PG} + Gt - \left(I_s * \frac{K_2 * PI}{K_{2m} + PI}\right) * PG, & (PI > PIT) \end{cases} \quad \text{Eq. 1}$$

2. Plasma Insulin:

$$\frac{dPI}{dt} = \begin{cases} K_4 - (d1 * PI), & (\underline{PG} < PGT) \\ K_4 - d1 * PI + \frac{K_5 * PG}{K_{5m} + PG} * (PG - PGT1), & (\underline{PG} > PGT) \end{cases} \quad \text{Eq. 2}$$

3. Brain glucose:

$$\frac{dBG}{dt} = \frac{K_8 * (PG - B\ \ )}{K_{8m} + (PG - B\ \ )} - K_{10} * BG \quad \text{Eq. 3}$$

Since brain forms only about 3 % of total body mass, we assume the reduction in plasma glucose diffused to the brain is a negligible fraction of total plasma glucose. Therefore, that term is not included in the plasma glucose dynamics. Similarly, insulin diffusion to brain is not represented in the plasma insulin dynamics. Nevertheless, the rate of plasma to brain diffusion is crucial in determining the brain glucose and insulin dynamics.

4. Brain insulin:

$$\frac{dBI}{dt} = \frac{K_9 * (PI - BI)}{K_{9m} + (PI - B\ \ )} - d_1 * BI \quad \text{Eq. 4}$$

At steady state (SS) all differential terms become zero and steady state levels can be calculated using equilibrium solutions.

As per the assumption of the model the brain needs a certain level of glucose and that is the target of homeostasis *BGt.* In order to ensure *BGt* at given K_8, K_{10} and K_{8m}, the SS plasma glucose *PG* needs to be

$$\underline{PG} = \frac{BG_t * K_{10} * K_{8m}}{K_8 - (\mathrm{BGt} * K_{10})} + \mathrm{BGt} \quad \text{Eq. 5}$$

438 We assume that the brain ensures this plasma glucose level by regulating liver glucose
439 production *L*. To maintain the desired plasma glucose level at steady state, the liver
440 glucose production should be:

441 $$L = \frac{K_1 * \underline{PG}}{K_{1m} + \underline{PG}} \quad \text{Eq. 6}$$

442 The brain can either ensure this by sending a calculated signal to the liver through the
443 autonomic system. Alternatively, this can be ensured by the brain by increasing
444 sympathetic inputs when *BG* <*BGt* and parasympathetic when it is above target (Antuna-
445 Puente et al., 2009; D'Alessio et al., 2001; Kiba, 2004). The required L can be achieved
446 iteratively by $L_{(t+1)} = L_{(t)} + K_s.(BGt - BG)$

447 Similarly, to ensure required brain insulin levels, plasma insulin should be

448 $$\underline{PI} = \frac{d_1 * BIt * K_{9m}}{K_9 - (d_1 * BIt)} + BIt \quad \text{Eq. 7}$$

449 To ensure this much plasma insulin level, K4 should be

450 $$K_4 = d_1.\underline{PI} \quad \text{Eq. 8}$$

451 Similar to glucose, the brain can ensure the target level of insulin in the brain by
452 neuronally modulating K_4 in a calculated or iterative manner. Specific autonomic inputs
453 are known to regulate β cell number as well as insulin release from β cells (Begg &
454 Woods, 2013; Boland et al., 2017; Kiba, 2004).

455 We also assume that both L and K_4 have a fixed upper limit as L_{max} and K_{4max} when the
456 maximum capacity of liver and pancreas is reached. L and K_4 cannot exceed this limit
457 even if neuronal inputs become more intense. This happens when K_8 declines below a
458 threshold such that,

459 $$K_8 < \frac{K_1 - L_{max}(BGt * K_{10*} K_{8m})}{L_{max} * K_{1m} - BGt(K_1 - L_{max})} - (BGt * K_{10}) \quad \text{Eq. 9}$$

460 There is a potential conflict here. Sympathetic tone is known to increase *L* (Nelles et al.,
461 1996; Nonogaki, 2000) whereas parasympathetic signal is required for proliferation of β
462 cells. Simultaneously sympathetic signal is known to inhibit insulin release from β cells
463 (Gilon & Henquin, 2001; Miller et al., 1976). If the brain is deficient in glucose as well as
464 insulin, both sympathetic and parasympathetic tones will be simultaneously higher (Watve

465 et al 2014). This is incorporated into the model by updating K_4iteratively according to both
466 BG and BI levels simultaneously,

467 $$K_{4(t+1)} = K_{4(t)} + K_p(BIt - BI) - K_s(BGt - BG) \quad \text{Eq. 10}$$

By
468 this consideration if sympathetic stimulation of liver glucose production is adequate to
469 restore required *BG*, $BGt - BG$ will tend to zero and there will be no interference in insulin
470 release by β cells. However, in case the rise in liver glucose production is inadequate to
471 ensure required *BG*, β cell function may be apparently affected.

472 <u>B. Simulating glucose tolerance curve</u>:

473 While for the steady state, equilibrium solutions can be algebraically derived, the post
474 glucose load curve and its properties can only be obtained by simulations. Simulations were
475 run using the same set of equations and giving a positive ephimeral Gt to simulate food
476 intake.
477 In all the simulations used, insulin resistance can be simulated by altering *Is*, β cell
478 dysfunction by reducing K_4 and/or K_5 and vascular defect slowing down transport of glucose
479 and insulin to brain and other organs by altering K_8, K_9 and K_1. Mental stress is assumed to
480 increase K_{10}. By differentially altering these parameters the model can separately and
481 collectively examine the effects of insulin resistance, β cell dysfunction and reduced rates of
482 diffusion across BBB on the glucose tolerance curve.
483

484 <u>T2DM- causal analysis</u>: We ask the question which minimal set of changes can give rise to
485 stable increase in fasting glucose, changes in the glucose tolerance curve characteristic of
486 type 2 diabetes along with other patterns listed above. The putative causal factors in are
487 examined individually and in combination. The factors include insulin resistance (Decreased
488 I_s), subnormal β cell response (Reduced K_4 *and/or* K_5), reduced insulin independent glucose
489 uptake (decrease in K_1), reduced blood to brain transmission of glucose (K_8) and insulin (K_9)
490 and stress related increase in brain glucose consumption (K_{10}). Subnormal or defective
491 vasculature is expected to decrease K_1, K_8 and K_9 proportionately, however the decrease in
492 the three parameters may not be proportionate if the vasculature in different parts of the
493 body is differentially affected. Also glucose transporters and there expressions can alter in

tissue specific manner. Therefore we allow proportionate as well as differential decrease in the three parameters.

Results:

A: Steady state solutions: We observed that the steady state solutions and the autonomic iteration simulations match well in the end result except when the limits of L and K_4 are reached. However, it took a long time to reach the desired level by iterative approach, particularly when the desired level was substantially different from the starting level. In real life major changes in vascular function or glucose transporter levels K_8, K_9, K_1 happen gradually. Therefore the desired level can be attained by autonomic fine tuning over time. Since in the iterative simulations, a long time was required to reach SS, we used the steady state solutions for quicker results.

It can be seen that the steady state levels of *PG* in the model is a stable steady state since substituting $PG < \underline{PG}$ leads to a positive value and $PG > \underline{PG}$ leads to a negative value of $\frac{dPG}{dt}$. The same applies to plasma insulin, brain glucose and brain insulin. This ensures a stable steady state of glucose-insulin in the plasma as well as brain on fasting [1,2]. From equations 5,6,7, and 8 we see that, *FG* does not change by altering *Is* or *FI*. This is compatible with the empirical findings that insulin receptor knockouts and insulin suppression experiments fail to increase fasting plasma glucose [9]. This result is unique to our model and is due to segregating fasting and post meal glucose regulation mechanisms. This is the only explanation offered so far, patterns [9], [16] and [17].

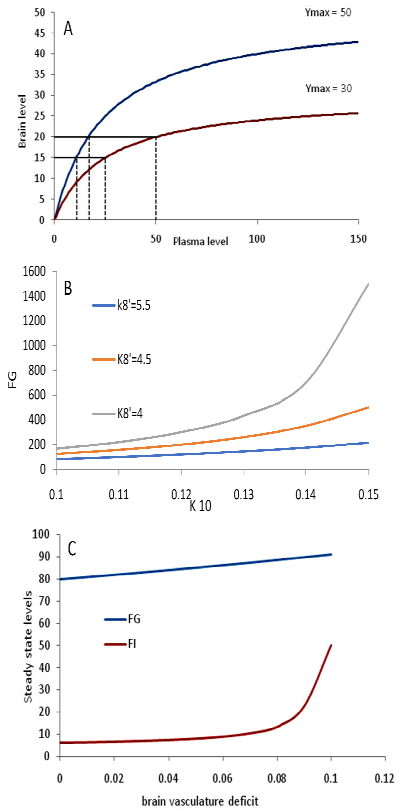
The steady state solution of our model shows that *FG* can increase as a result of increase in K_{10} or decrease in K_8. That is if the glucose consumption in brain increases and/or the rate of glucose transport from blood to brain decreases. Both the effects are interdependent and the shape of the glucose response is decided by the interaction between K_8 and K_{10}. Increased K_{10} increases *FG* marginally and almost linearly when K_8 is large. When K_8 decreases even a marginal rise in K_{10} can induce disproportionately greater rise in *FG* (fig 1). This means that stress induced hyperglycemia is unlikely to be seen in healthy individuals while it is more likely in individuals with reduced vascular transport [7].

Figure 1: The same input different output (SIDO) phenomenon:

A. *A conceptual diagram with arbitrary units: A saturation relationship in glucose and insulin transport has important consequences that can account for many phenomena observed in prediabetic and diabetic stages. For example here for achieving an increase in Y by 6 units with a higher Ymax, X needs to increase only by 6 units but at a lower Ymax for the same target increase in Y 25 units of increment in X is needed. This non-linearity explains many phenomena including prediabetic hyperinsulinemia and stress induced diabetes in our model of glucose homeostasis.*

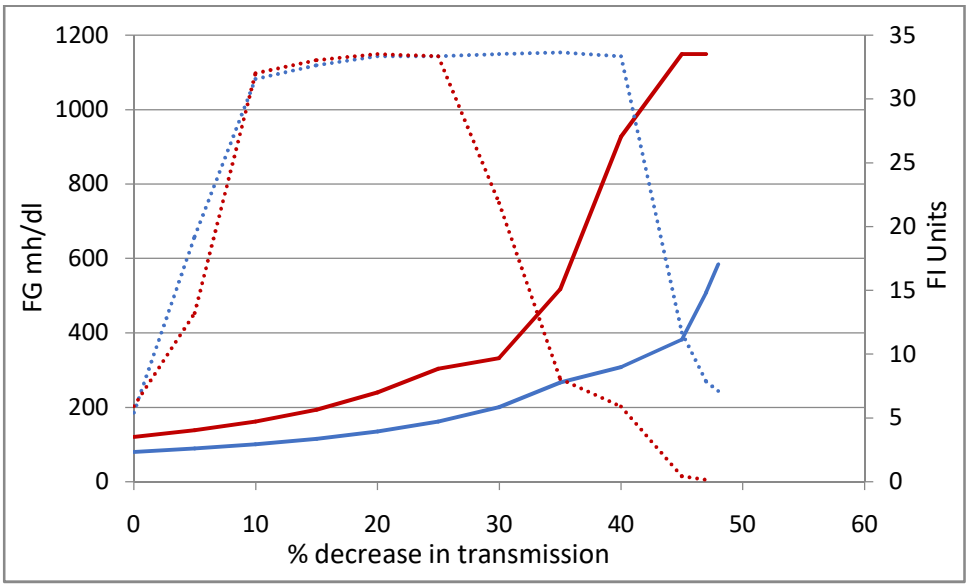
B. *A simulation using the steady state model: It can be seen that as K_8 decreases, for the same change in brain requirement K_{10}, a non-linear escalated increase in plasma glucose is required.*

C. *A simulation result assuming a correlated decrease in K_8 and K_9 which is expected if the underlying cause is reduced brain vasculature. It is possible that while glucose shows a marginal increase, insulin increases substantially, since the parameters of glucose and insulin transport curves are different. This is a potential explanation for hyperinsulinemic normoglycemic state.*



The origin of hyperinsulinemic normoglycemic condition can be explained by the difference in the parameters of the saturation curves of transport dynamics of glucose and insulin. If the insulin diffusion is assumed to be nearer to saturation and glucose diffusion is sufficiently away from saturation, at the same level of vascular function deficiency, insulin will increase disproportionately more than glucose (Figure 1). This is a possible cause of hyperinsulinemic normoglycemic state [3], and the reason why hyperinsulinemia precedes hyperglycemia [4] which requires neither insulin resistance nor compensatory hyperinsulinemic response. When this happens the HOMA-IR and HOMA β increase although there is no change in true insulin resistance and compensatory insulin response. This gives a false impression of insulin resistance as defined popularly.

Further as the transport saturation constant K_8 and K_9 continue to decrease proportionately, *FG* increases monotonically but *FI* shows a non-monotonic curve in which *FI* increases with moderate decrease in transport rates but decreases after a threshold decrease in transport rates. This non-monotonicity is predicted by the iterative autonomic inputs model. When the required *L* approaches or exceeds L_{max}, the steady state *BG* remains smaller than *BGt*. The resultant increase in the sympathetic signal inhibits insulin release from β cells. This leads to reduced insulin secretion and insulin levels drop substantially. Thus, without bringing in additional factors the model explains the early phase rise in fasting insulin as well as the later phase decline in the course of T2DM [4] (Figure 2).



562 *Fingure2: Effect of correlated decrease in K_8 and K_9 on fasting plasma glucose and insulin.*
563 *Note that for a small to moderate decrease FI increases rapidly with marginal change in FG.*
564 *However after a threshold decrease in the transport rates FI declines sharply whereas FG*
565 *increases rapidly. This pattern matches with the course of clinical T2DM without involving*
566 *insulin resistance, compensatory hyperinsulinemia and β cell exhaustion. Simulation specific*
567 *other parameters were K_{1m} =50, K_1=30, K_{2m}=15, K_2=0.01, K_{5m}=0.01, K_5=0.5, d_1=0.15, I_s=1,*
568 *BGt=25, BIt=5, K_{8m}=80, K_8=5, K_{9m}=0.3, K_9=0.8, K_{10}=0.1(Blue line) and 0.12(Red line).*

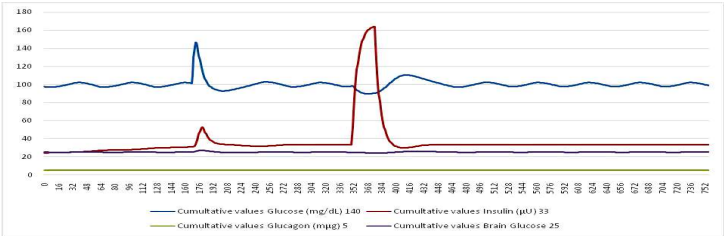
569 This decline in the insulin response does not require β cell dysfunction as a causal
570 mechanism but there are more complex possible effects on β cells. Simultaneous activation
571 of sympathetic and parasympathetic inputs to β cells is implicated in β cell amyloidogenesis
572 (Watve et al., 2014). Parasympathetic stimulation is known to increase β cell number.
573 However, sympathetic signaling suppresses insulin release resulting in increased retention
574 time of insulin along with amylin which beyond a threshold retardation results in to
575 spontaneous polymerization of amyloid protein leading to poisoning of β cells and
576 amyloidogenesis (Watve et al., 2014). This is an alternative causal interpretation of β cell
577 dysfunction and decline in its population. This mechanism has a built-in negative feedback
578 loop giving rise to a steady state β cell population. This result is compatible with the finding
579 in which the β cell population remains subnormal lifelong [11,12]. This contrasts the
580 dynamics expected by the classical thinking in which β cells are destroyed by gluco-
581 lipotoxicity or oxidative stress. This mechanism has a built-in positive feedback cycle. As a
582 part of the β cell population is destroyed, the insulin secretion is decreased which would
583 increase glucose further accelerating gluco-lipotoxicity and oxidative stress and thereby β
584 cell loss. Such a positive feedback vicious cycle can only stop with complete destruction of
585 the β cell population. This prediction of the classical model does not match the finding of
586 sustained presence of subnormal β cell population in T2DM.

587 By the classical model, prolonged sustained exercise in the fasting state should result into
588 lower plasma glucose. However, experimental increase in glucose uptake resulting from
589 physical activity during fasting does not necessarily result into a decrease in *FG*. This is
590 mainly because as *FG* starts decreasing, *BG* decreases consequently. *BG* being lower than
591 the brain target induces sympathetic mediated increase in *L* and the change in *FG* by
592 physical activity is more or less compensated. This may happen through the agency of

glucagon as well, since a strong link between autonomic signals and glucagon secretion is known. Therefore, at times plasma glucose may actually increase after intensive exercise. Further, if exercise involves heightened activation of cerebellar mechanisms of coordination K_{10} can also increase resulting into higher rather than lower *FG* in response to exercise [8].

A high dose of exogenous insulin results into increased plasma glucose after a time lag, is known as Somogyi phenomenon. The phenomenon is conditional and not seen in every diabetic. It is said to involve the counter-regulatory response on facing central hypoglycorrhachia. However, often this response is seen without peripheral hypoglycemia. This is best explained by reduced K_8 that gives rise to decreases *BG/FG* ratio. With smaller K_8, at apparently normal or increased plasma glucose, brain glucose can still be lower than the target which gives a sympathetic signal to increase *L*. Simulations using the autonomic iteration model shows this phenomenon quite well at low K_8. At the same level of insulin infusion, at lower K_8 there is more intense hyperglycemic response (Figure 3) [14]. A model without accommodating changes in K_8 does not predict Somogyi phenomenon without an obvious hypoglycemic state.

At transmission 90%



At transmission 70%

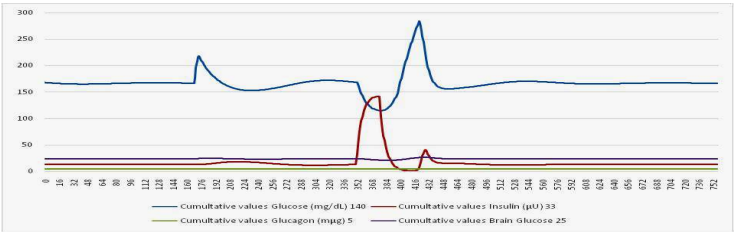


Figure 3:Effect of high dose insulin on peripheral glucose under two rates of glucose and insulin transport across the blood brain barrier (Correlated decrease in K_8 and K_9). A paradoxical rise in blood sugar following insulin administration is more prominent when the transport rate is substantially lower than normal. Other parameters (K_{1m} =50, K_1=30, K_{2m}=15,

616 K_2=0.08, K_{5m}=0.01, K_5=15, d_1=0.15, I_s=1, BGt=25, BIt=4.5, K_{8m}=80, K_8=5, K_{9m}=0.3, K_9=0.8,
617 K_{10}=0.1)

618 The response is restricted to a narrow set of conditions. For intense hyperglycemic response
619 to insulin administration, it is necessary that insulin sensitivity is good, *BG* is close to *BGt*
620 before insulin transfusion, and K_8 is subnormal.

621 Potentially one can visualize two distinct possible classes of reasons why blood sugar
622 increases in response to brain injury. In the first, there is some impairment in the glucose
623 regulation mechanism. In the second, the requirement for glucose is increased during the
624 wound healing process and hyperglycemia is a mechanism of the body to meet the demand.
625 It is known that infections such as meningitis, stroke or hemorrhage leads to transient
626 hyperglycemia. Such hyperglycemia is often accompanied by lower *BG* levels (Schut et al.,
627 2009; van Veen et al., 2016)[15]. In such cases, hypoglycemic treatments can be
628 counterproductive and result into delayed or derailed repair process. This is a likely reason
629 why in patients under intensive care, strict regulation of plasma glucose increased mortality
630 instead of the expected decrease (The NICE-SUGAR Study Investigators, 2009).

631 When hyperglycemia is a process of meeting increased glucose demand or compensating
632 subnormal transport, removal of plasma glucose by any means is expected to increase *L*.
633 This is observed to happen when SGLT2 inhibitors decrease the urinary threshold and drive
634 out plasma glucose. If increasing *L* is not sufficient to restore the required glucose level,
635 there is a shift to ketogenesis since the brain can use keto acids as alternative source of
636 energy.Therefore, increased *L* with or without increased ketogenesis is expected following
637 SGLT2 inhibitors [13].

638 <u>B: Glucose tolerance curve</u>: Unlike the steady state predictions, the patterns of post feeding
639 glucose curve by our model are not qualitatively different from classical models. The area
640 under the curve, height of the peak, time required to return to steady state and the time
641 difference between glucose and insulin peaks are increased by decreased I_s , K_4 or K_8
642 individually or in combination. Decrease in I_s or K_4 secretion does not increase *FG* but
643 changes the shape of the glucose tolerance curve. Decreased K_8 may alter both
644 simultaneously. The altered curve shows the three typical features namely taller peak,
645 delayed return to steady state and longer gap between glucose peak and insulin peak [5].

646 This result is not unique to our model and classical models also show the three features. The
647 classical model results into simultaneous and proportionate alterations in the fasting as well
648 as post meal glucose by changing I_s or K_4 and therefore fails to explain the NFG-IGT state. In
649 our model, decreasing I_s or K_1 without a change in K_8 results into a NFG-IGT state [6].

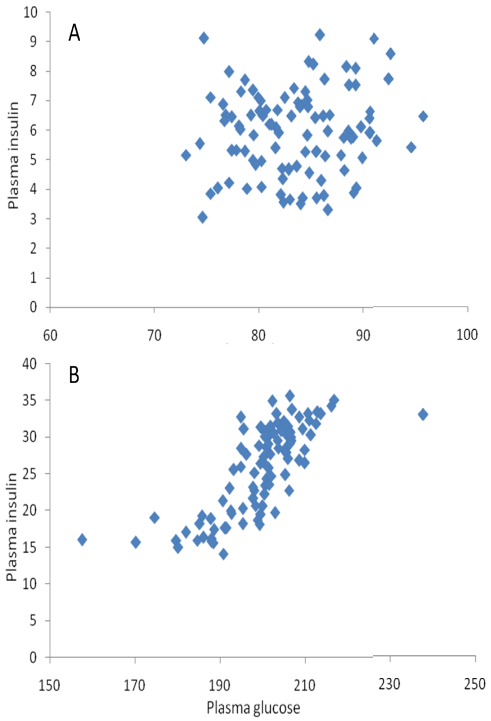
650

651 <u>C: Population simulations</u>: For the steady state as well as post glucose load dynamics we
652 give population distributions to K_1, K_5, K_8, K_9, I_S and also incorporate normally distributed
653 error in glucose and insulin measurements in fasting and post meal sampling. We also
654 incorporate correlated changes in K_1, K_8 and K_9 which are expected as a result of hypo-
655 vascularization in the brain. These simulations are run to observe whether we get the
656 anomalous correlations in fasting versus post meal state and in the HOMA indices as
657 observed empirically (Chawla et al., 2018, Diwekar-Joshi and Watve 2020).

658 By classical models the regression correlation parameters of glucose-insulin relationship are
659 not different in fasting state versus post glucose load although the range of variables is
660 different as shown previously by Diwekar-Joshi and Watve (2020). Also, if we assume
661 HOMA-IR to faithfully reflect insulin resistance and HOMA β to faithfully represent β cell
662 response, then there is no reason why the two indices should be correlated.

663 The assumption behind our model that there are different mechanisms at work under
664 fasting versus post glucose load condition is necessary to explain the large difference in the
665 regression correlation parameters in fasting versus post meal levels. If the same set of
666 mechanisms in the fasting and post meal conditions are operational, whatever the model
667 used, it is imperative that fasting correlation regression parameters are stronger or similar
668 to post meal parameters. Simulations with our model are able to give poor *FG-FI* correlation
669 along with strong post meal glucose insulin correlation under multiple conditions [16]
670 (Figure 4). When the variance in K_8 and K_9 is small but that in K_1, K_5, Gt and I_s individually or
671 in combination is large, the fasting correlations are weak and post meal correlations strong;
672 the post meal glucose-insulin regression slope is substantially greater than *FG-FI* slope. Also,
673 whenever *FG-FI* correlation is weak, the indices HOMA-IR and HOMA β are strongly
674 correlated similar to the epidemiological data [17]. The difference between fasting and post
675 meal regression correlation patterns is not predicted by the classical models and is unique

676 to our model which assumes different set of regulatory mechanisms in the fasting and post
677 meal state.

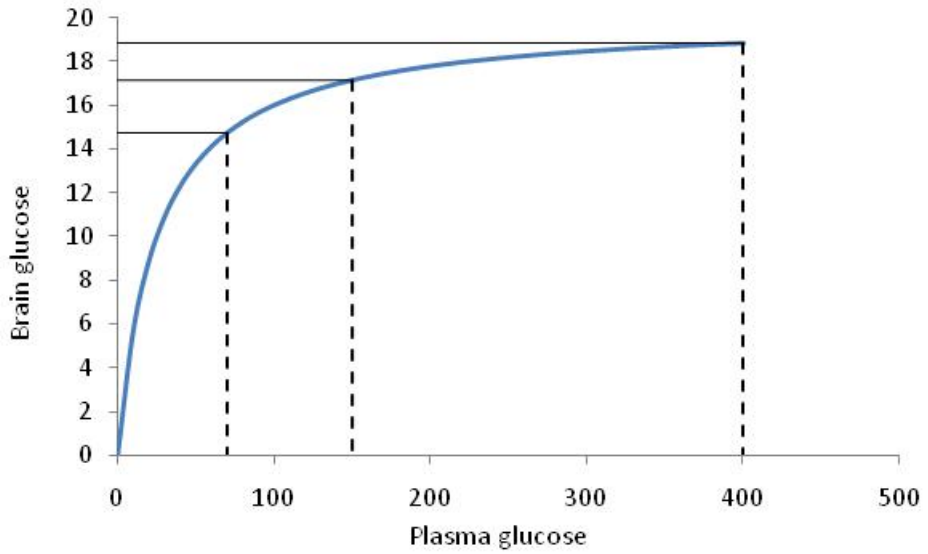


678

679 *Figure 4: Plasma glucose and insulin correlation in the fasting steady state (A) and post meal*
680 *(B) in simulations. The empirical finding that there is a strong positive correlation in the post*
681 *meal data (R^2=0.57) but poor correlation in fasting steady state (R^2=0.014) was possible*
682 *under a variety of conditions in our model. Depicted here the simulation results in which K_1*
683 *was given a wider population distribution mean (S.D.) K_1 = 35(7)and K_5 = 10(0.00001), K_8 =*
684 *5(0.000005), and K_9 = 0.8(0.000008) had a narrow distribution. Other parameters (K_{1m} =50,*
685 *K_{mum}=15, K_2=0.05, d_1=0.15, I_s=1, BGt=25, BI=4.5, K_{8m}=80, K_{10}=0.1).*

686 <u>D: Effect of glucose normalization on arresting diabetic complications and mortality</u>: By
687 classical thinking, chronic hyperglycemia is responsible for the diabetic complications and
688 preventing hyperglycemia should arrest complications. In contrast the thought behind our
689 model is that vascular problems are primary which alter the rate of glucose insulin transport
690 to the brain and hyperglycemia is an offshoot symptom that may not be causal to diabetic
691 complications which can arise directly from the vasculopathy. Therefore, controlling glucose
692 may not have any effect on diabetic complications [18]. On the other hand forcefully
693 reducing plasma sugar without addressing vascular problems can create more severe
694 glucose deficiency in the brain and other organs, thereby turning counterproductive.

695 Because of the saturating dynamics of transport, a curvilinear relationship is expected
696 between plasma glucose and brain glucose in such a way that moderate reduction in
697 hyperglycemia will change brain glucose availability marginally whereas tight glucose
698 regulation can have disproportionately larger effect (Figure 5). Therefore, tight glucose
699 regulation may increase mortality and other adverse outcomes. This prediction is
700 compatible with some of the tight versus moderate control clinical trials including ACCORD,
701 NICE sugar trial and UGDP [18].



702

703 *Figure 5: Effect of glucose lowering on brain glucose availability. For example, a reduction in*
704 *FG from 400 mg/dl to 150 mg/dl corresponds to a decrease in BG of 1.68 mg/dl, but further*
705 *reduction from 150 to 70 mg/dl reduces BG by 2.41 mg/dl. Therefore a moderate sugar*
706 *control may not affect brain glucose supply drastically but tight sugar control is expected to*
707 *affect it more seriously.*

708 **Discussion**:

709 The main inference from our model, stated most conservatively, is that a brain centered
710 model can potentially explain most of the anomalies faced by peripheral models and
711 therefore needs greater attention. If supported well, by exploring its testable predictions
712 suggested below and possibly more, it has a potential to bring in a radical change in the
713 fundamental view as well as clinical practice of T2DM.

714 <u>Testability of assumptions and additional predictions</u>:

The assumption that the thresholds *PGT* and *PIT* can be modified by autonomous signaling needs to be tested empirically. Although currently the thresholds are known to be flexible, information about the conditions and mechanisms of change are poorly known.

The assumption of our model that reduced transport of glucose and insulin to brain is the primary pathology of T2DM leading secondarily to hyperglycemia makes more predictions that can be tested experimentally or epidemiologically. Experimentally specifically blocking glut1 receptors in the brain should lead to hyperglycemia. Conversely infusion of glucose directly to the brain should reduce peripheral hyperglycemia in the short run. This is already suggested by some experiments (Ono et al., 1983; Osundiji et al., 2012). It is also demonstrated that inducing primary endothelial dysfunction and reduced glucose transport to brain by endothelial deletion of hypoxia inducible factor HIF-1α results in hyperglycemia (Huang et al 2012). More careful research in this direction to reveal the cause effect relationship between vascular defects, brain glucose levels and plasma glucose levels will be enlightening. Epidemiologically hypoglycemia is shown to associate with dementia and other neuronal problems (Lipska and Montori 2013, Meneilli and Tessier 2016, Rhee 2017, Yaffe et al 2013), tight glycemic control led to higher mortality as compared to moderate control in many of the clinical trials (Klein 2010, Schwartz & Meinert, 2004, The NICE-SUGAR Study Investigators, 2009) which demands investigations into the causal pathways. The question whether tight glycemic control leads to subtle neuronal changes in the long run as expected by our model needs careful investigation. The difference between fasting and post meal regression correlation parameters between glucose and insulin is an important epidemiological line of evidence we have used. Chawla et al (2017) and Diwekar-Joshi and Watve (2020) showed this pattern across four different data sets. How generalized the pattern is can be easily tested in multiple populations.

On the modeling front it is necessary to undertake comparative evaluation of the different models with respect to the battery of prediction that we listed here. Perhaps a few more predictions may be added. However, at present many of the models and their possible modifications are not explored sufficiently to see whether they can explain the currently unexplained patterns under certain set of conditions. A model prediction matrix would be an appropriate approach for such a comparative evaluation, but we may have to wait till all alternative models are explored sufficiently elaborately on which of the empirical patterns

746 they predict, which ones they are compatible with and which ones they contradict. We have
747 shown here that the brain centered model predicts or is compatible with all the patterns
748 listed in the introduction and does not contradict any.

749 Possible causes of T2DM:

750 The classically believed causal factors namely insulin resistance and β cell dysfunction are
751 not compatible with many of the empirical findings as shown by Diwekar-Joshi and Watve
752 (2020). In our model change in insulin resistance and β cell dysfunction were neither
753 necessary nor sufficient to account for all the patterns. Nevertheless they were helpful in
754 accounting for the altered glucose tolerance curve, although other factors could also
755 account for it independent of insulin resistance. Incorporating insulin resistance in our
756 model and assuming it to work only in the post feeding state, patterns 1,2,5,6,9,16 and 17
757 could be explained but not others. In short, our model does not rule out insulin resistance as
758 a phenomenon, but implies that it may not be central to T2DM. Primary vasculature
759 impairment reducing glucose and insulin transport in mutually correlated or uncorrelated
760 manner could explain all patterns and therefore makes the most parsimonious causal
761 hypothesis. B cell dysfunction is an inevitable effect of higher degree of vascular dysfunction
762 and therefore may not be needed as an independent causal factor.

763 Being open to alternative possibilities is an important virtue of science and it is particularly
764 important when the mainstream thinking has limited success and mounting anomalous
765 findings. Prevention of T2DM on a global scale has largely failed and treatment has limited
766 and inconsistent success in arresting mortality and morbidities associated with T2DM
767 (Brown et al., 2004; DeFronzo, 2010; Rosengren et al., 2008, Lee et al 2021). Therefore,
768 exploring alternative possible interpretations is a need of the time.

769 Triggered by multiple anomalies in the theory of glucose homeostasis and the origins of
770 diabetic hyperglycemia, we have articulated here an alternative paradigm which potentially
771 resolves in a logically and mathematically consistent manner many of the anomalous
772 findings. Being mathematically and logically sound and compatible with evidence is not a
773 proof of a theory but certainly reflects on its potential to develop into a new alternative
774 paradigm. For a large field such as T2DM multiple efforts would be needed to evaluate
775 competing paradigms. We have suggested a few more testable predictions that can help in

776 this task. There can be more possible ways of testing them which should come to light and
777 used to reach robust conclusions which have the potential to change the clinical course of
778 prevention as well as treatment of an important global health problem.

779 If our proposed causal inference that vascular dysfunction is primary to T2DM is supported
780 by more careful investigations, it explains the failure of glucose normalizing treatment in
781 arresting diabetic complications. Simultaneously it suggests alternative lines of treatments
782 which should focus on normalizing vascular and neuronal function rather than focusing on
783 glucose normalization. The deficiencies of stimuli normally required for growth factors and
784 other angiogenic and neuroprotective factors can be forecasted as the best bet for the new
785 approach. However, rigorous efforts are needed to strengthen the evidence base for
786 selecting the right one amongst the alternative paradigms.

787

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