Qeios

1   Reduced blood to brain glucose transport as the cause for hyperglycemia: a model that

2   resolves multiple anomalies in type 2 diabetes

3   Akanksha Ojha,

4   Indian Institute of Science Education and Research, Pune,

5   Pune, 411008

6   India

7   akanksha.ojha@students.iiserpune.ac.in

8

9   Milind Watve,*

10   Independent Researcher,

11   E-1-8, Girija Shankar Vihar,

12   Karve Nagar, Pune 411052, India

13   milind.watve@gmail.com

14

15   * for correspondence

16   Reduced blood to brain glucose transport as the cause for hyperglycemia: a model that

17   resolves multiple anomalies in type 2 diabetes

18

19   **Abstract:**

20   Classically, type 2 diabetes is believed to be a result of insulin resistance and relative insulin

21   deficiency. However, evidence has been accumulating against the insulin resistance models.

22   Absence of lasting hyperglycemia by insulin receptor knockouts or insulin suppression,

23   evidence for hyperinsulinemia preceding insulin resistance, the perplexing hyperinsulinemic

24   normoglycemic state, reduced glucose transport to the brain preceding hyperglycemia, signs

25   of vasculopathy preceding hyperglycemia, absent or poor correlation between fasting

26   glucose and insulin, very strong positive correlation between indices of insulin resistance

27   and β cell function in population data are some of the anomalous findings which classical

28   glucose homeostasis models have not addressed so far. With increasing evidence for

29   neuronal involvement in glucose regulation, we propose a refined model of glucose

30   regulation that considers brain glucose and insulin levels as the ultimate target of

31   homeostasis and combines central and peripheral mechanisms of regulation. A model

32   considering the reduced rate of blood-to-brain transportation of glucose and insulin as

33   primary pathology explains most of the patterns, with or without insulin resistance. Apart

34   from resolving multiple anomalies, the model also accounts for the failure of glucose

35   normalization in effectively reducing diabetic complications and mortality.

1. Introduction

Presently, any metabolic disorder with consistently raised plasma glucose and insulin resistance, which cannot be categorized into either type 1 diabetes or gestational diabetes, is defined as type 2 diabetes mellitus (T2DM) (DeFronzo et al., 2015). It is the most common form of diabetes, accounting for over 90% of all cases. The classically perceived cause of hyperglycemia in T2DM is insulin resistance followed by failure of compensatory insulin response. Historically, the role of the 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 (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-centred 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 & Wheatve, 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 signalling or fasting insulin levels 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) failed to alter fasting glucose in the expected direction. 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 classical models. With converging multiple lines of evidence, Diwekar-Joshi and Watve (2020) raised doubts about 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 the liver. One of the foundational assumptions is that both the above processes are regulated by insulin signalling in the steady state (Matthews et al., 1985). Therefore, insulin signalling 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-centred model further, incorporating recent evidence, evaluate its performance in explaining the accumulated anomalies and explore its physiological and clinical implications.

1.1 <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 levels and the alterations in the glucose curve in the prediabetic and diabetic states. 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 comparing alternative models. Such an approach has been used to test alternative hypotheses in a number of other contexts (Shinde et al., 2021; Thakar et al., 2003; Vibishan & Watve, 2020; Watve & Diwekar-Joshi, 2016), and it can be the right approach to test

98   alternative models of glucose homeostasis in T2DM. A model of choice would be one which

99   can predict all or most of the known physiological patterns in type 2 diabetes so that no or

100 minimal anomalies are left. We take a few steps towards a model prediction matrix,

101 although a lot more exploration of many other models is required before constructing such

102 a matrix.

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

104 1. The model should allow stable, steady state glucose on fasting: Fasting glucose is
105   assumed to be a steady state with adequate evidence (Lerner & Porte, 1972;
106   Matthews et al., 1985; R. C. Turner et al., 1979). Achieving a steady state is one of
107   the primary objectives of every homeostasis model. Many of the key concepts of
108   classical models are also based on achieving a steady state in the fasting condition
109   (Matthews et al., 1985; R. C. Turner et al., 1979).

110 2. The model should also allow stable, steady-state insulin on fasting. Normally, this is
111   not a problem for any model; however, many models have a problem explaining the
112   altered steady-state insulin level in a prediabetic state, as explained below.

113 3. Prediabetic state of normoglycemia with hyperinsulinemia: A prediabetic state is
114   often accompanied by a high level of fasting insulin (FI) but normal fasting glucose
115   (FG) in the plasma. This is not easy to achieve in a model. The classical qualitative
116   explanation of this state is that it is a state of insulin resistance with a compensatory
117   rise in FI such that FG remains normal. For this to happen, there is a need to
118   estimate the level of insulin resistance and regulate insulin secretion accordingly. It is
119   possible to hypothesize a mechanism for sensing insulin resistance and conveying
120   this information to the pancreas. Such a mechanism can be glucose-dependent or
121   glucose-independent. Currently, no glucose-independent mechanism for accurately
122   assessing insulin resistance and conveying it to β cells is known. A common
123   assumption is that insulin resistance reduces glucose uptake, thereby increasing FG.
124   The rise in FG stimulates insulin production, and the rise in insulin levels normalizes
125   glucose again. However, this mechanism fails to achieve a steady state of
126   hyperinsulinemic normoglycemic condition (Diwekar-Joshi & Watve, 2020). Plasma
127   insulin has a short half-life, and after glucose levels are normalized, it is unlikely to
128   stay at a higher level unless there is a glucose-independent trigger for insulin

129   secretion. Explaining a hyperinsulinemic normoglycemic steady state is a tricky

130   challenge that any model needs to meet.

131   4. Hyperinsulinemia precedes insulin resistance and T2DM: Although hyperinsulinemia

132   is believed to be a compensatory response to insulin resistance, a number of studies

133   show that hyperinsulinemia precedes obesity and insulin resistance (Corkey

134   &Shirihai, 2012; Mehran et al., 2012a; Pories & Dohm, 2020; Shanik et al., 2008;

135   Weyer et al., 2000; Wiebe et al., 2021). This raises two independent questions. One

136   is how and why hyperinsulinemia precedes insulin resistance. The second, more

137   perplexing question is that if hyperinsulinemia is not a compensatory response to

138   insulin resistance, the failure of compensation explanation becomes redundant. This

139   needs to be replaced by a more coherent explanation of hyperglycemia.

140   5. The model should explain the following features of the post-meal glucose curve and

141   its alterations in prediabetic and diabetic states, which cumulatively are called

142   impaired glucose tolerance curves.

143   a. Increased height of peaks

144   b. Delayed return to normal

145   c. An increase in the time difference in glucose and insulin peaks in the diabetic

146   state.

147   6. The normal fasting glucose with impaired glucose tolerance (NFG-IGT) state: It is

148   common to find that in a prediabetic state, the glucose tolerance curve is altered

149   with a normal level of fasting glucose.

150   7. Stress hyperglycemia: Why and how stress causes hyperglycemia only in some

151   individuals (Dungan et al., 2009) needs to be explained by a model with realistic and

152   testable assumptions.

153   8. Hyperglycemia after intensive exercise: If in a fasting state, *FG* is a result of the rate

154   of liver glucose production and glucose disposal, an exercise that increases glucose

155   disposal should decrease *FG*. However, in some studies, plasma glucose remains

156   unchanged or is increased after exercise (Coggan, 1991; Marliss & Vranic, 2002). A

157   model needs to predict this result contextually.

158   9. An important challenge is to explain why insulin receptor knockouts specific to

159   muscle, fat cells or the liver result in normal fasting glucose but altered post-glucose

160   load curves. Similarly, insulin-degrading enzyme knockouts do not alter *FG*. Also,

161   insulin suppression by agents such as octreotide or diazoxide fails to alter *FG*

162   (Diwekar-Joshi & Watve, 2020). A model should explain these observations. Diwekar-

163   Joshi and Watve (2020) further differentiated between the consequential steady

164   state (CSS) and targeted steady state (TSS) models and demonstrated that the results

165   of the insulin receptor knockout and insulin suppression experiments can be

166   explained by a TSS but not by a CSS model. In effect, to be able to account for these

167   results, a model needs to be a TSS model.

168   10. Reduced glucose transport to the brain, particularly in obese or prediabetic

169   individuals: It has been known over a long time that in type 2 diabetes, the rate of

170   glucose transport from blood to the brain is slowed down substantially (Gjedde &

171   Crone, 1981). In rodent models, the glut-1 expression in brain capillaries is shown to

172   be reduced (Cornford et al., 1995; Matthews et al., 1985; Pardridge et al., 1990). This

173   has been viewed as a response to hyperglycemia. However, Hwang et al. (2017)

174   show that subnormal transport is evident in obese and presumably prediabetic

175   states, even before hyperglycemia appears. A model needs to account for this

176   pattern as a causal or consequential phenomenon.

177   11. The T2DM-specific islet amyloid deposition, which often accompanies islet

178   deterioration: Islet amyloid deposition is frequently associated with type 2 diabetes

179   but not observed in type 1. The causes of islet amyloid deposition should be

180   compatible with the glucose homeostasis model (Höppener et al., 1999; Porte &

181   Kahn, 1989; Watve, 2014).

182   12. B cell deterioration pattern: The deterioration of β cells appears to follow a peculiar

183   pattern in T2DM, in which a substantial proportion of β cells survive lifelong (Bacha

184   et al., 2013; Butler et al., 2003; Clark et al., 2001; Porte & Kahn, 2001; Watve, 2014).

185   If dysfunction and damage to the β cell population are assumed to be an essential

186   prerequisite of hyperglycemia in a model, the models need to account for the

187   peculiar population dynamics of β cells.

188   13. Increased liver glucose production as well as ketogenesis with SGLT2 inhibitors: Over

189   the last decade, SGLT2 inhibitors, which allow greater clearance of glucose through

190   urine, have offered a novel means of combating hyperglycemia. Lowering of plasma

191   glucose by SGLT2 inhibitors is accompanied by increased liver glucose production as

192   well as increased ketogenesis (Limenta et al., 2019; Mistry & Eschler, 2021; Op den

193   Kamp et al., 2021; Pfützner et al., 2017) The causes of which should be made clear by
194   the model.

195   14. The Somogyi phenomenon, i.e., hyperglycemia following infusion of insulin, is seen
196   in at least some cases of T2DM but not in healthy individuals. This can happen
197   without being overtly hypoglycemic (Campbell, 1976; Reyhanoglu & Rehman, 2021).

198   15. In cases of brain injury, hyperglycemia is common (Shi et al., 2016). In bacterial
199   meningitis, hyperglycemia is often observed, accompanied by low CSF glucose levels
200   (Krishnan et al., 2016; Schut et al., 2009). A model should be able to account for the
201   apparent contradiction.

202   16. In population data, one sees a good correlation between post-meal glucose and
203   insulin but a poor correlation between *FG* and *FI* (Diwekar-Joshi & Watve, 2020).

204   17. Although FG and FI are poorly correlated in prediabetic states, HOMA-β and HOMA-
205   IR have strong positive correlations in population data (Diwekar-Joshi & Watve,
206   2020).

207   18. Failure of glucose normalization to reduce the frequency of complications and
208   mortality: Unlike T1DM, in T2DM, tight regulation of plasma glucose has failed to
209   show a reduction in mortality consistently across multiple large-scale clinical trials
210   (Diabetes Prevention Program Research Group, 2015; Ferrannini & DeFronzo, 2015;
211   King et al., 1999; Klein, 2010; Lee et al., 2021; Schwartz & Meinert, 2004; R. Turner et
212   al., 1998; The NICE-SUGAR Study Investigators, 2009, UK Prospective Diabetes Study
213   (UKPDS) Group, 1998). If hyperglycemia is the primary pathology of type 2 diabetes,
214   preventing or correcting it should have reduced the frequency of complications and
215   mortality considerably.

216   19. Reversal of hyperglycemia by FGF 21 in all models of rodent diabetes: Independent
217   of the cause of hyperglycemia, a single injection of FGF 21 was able to achieve long-
218   term normalization of plasma glucose (Laeger et al., 2017).

219

220 While most models intend to explain 1, 2 and 5 of the above, they either fail to explain or do

221 not address the others. Our expectation from a satisfactory model is that it should

222 inherently predict these outcomes or should be compatible with them. If an additional

223 explanation that does not contradict the model accounts for the phenomenon, the model

224 can be said to be compatible. Compatibility with empirical findings cannot be taken as proof

225 or validation of the model, but if a model directly contradicts one or more of the empirical

226 findings, it becomes serious grounds for rejecting the model. Later, when we describe model

227 results, we will use the numbers in the above list in square brackets to indicate that the

228 model accounted for this pattern.

229 1.2 <u>Peripheral models of glucose homoeostasis:</u>

230 There is a rich history of the development of mathematical models of glucose homeostasis

231 and the origin and progression of type 1 and type 2 diabetes (reviewed by Ajmera et al.,

232 2013; Mari et al., 2020). The focus of the field is so much on the peripheral mechanism that

233 the review by Mari et al. (2020) does not even cite the models incorporating the role of the

234 brain. Ajmera et al. (2013) briefly mention the Gouhua et al. (2009) model but do not

235 elaborate on its potential implications. A class of models attempts to capture glucose

236 homeostasis at the systems levels, whereas other models look at individual components

237 such as insulin-dependent glucose uptake, liver glucose production, β cell dysfunction,

238 glucose-stimulated insulin secretion and incretin effects in greater detail. Nevertheless,

239 these models together have not accounted for the majority of the patterns listed above. The

240 central assumption of these models is more or less invariant and revolves around insulin

241 resistance and the failure of insulin response to adequately compensate for it (Mari et al.,

242 2020). Diwekar-Joshi and Watve (2020) claimed that any model with this set of assumptions

243 is not compatible with empirical patterns 3,4,6,9, 16 and 17 of the above. Whether any

244 variation of these models can do so has not been adequately explored. Furthermore, all the

245 peripheral regulation models are CSS models in that the fasting steady state is a

246 consequence of the rate of liver glucose production and a concentration-dependent rate of

247 glucose uptake. In these models, a change in either or both the rates inevitably alters the

248 steady state. This contrasts the TSS models in which alteration in these rates alters the time

249 required to reach a steady state but does not alter the steady-state glucose level (Diwekar-

250 Joshi & Watve, 2020). An attempt to develop a TSS model with only peripheral mechanisms

251 has not been made to the best of our knowledge.

252 We do not intend to review glucose homeostasis models here. However, we observe from

253 published reviews of glucose homeostasis models (Ajmera et al., 2013; Mari et al., 2020)

254 that most models do not address the apparently anomalous empirical findings, particularly

255 3,4,6,9,10,11,12,13 and 15-18 among the ones listed above. A detailed exploration into

256 whether some variations of these models can address the apparently anomalous patterns is

257 beyond the scope of this paper, but we remain open to this possibility.

258 1.3 <u>Brain-centered models of glucose homeostasis</u>**:**

259 It is quite well known that a number of neuronal mechanisms in the brain are involved in

260 energy homeostasis. Nevertheless, for some reason, they do not occupy a central stage in

261 the mainstream thinking in T2DM and glucose regulation models. A number of recent

262 publications highlight the role of the brain in different ways (Lam, 2005; Osundiji et al.,

263 2012; Perrin et al., 2004; Watve, 2013; Lundqvist et al., 2019). Peters (2004), Gaohua and

264 Kimura (2009) and Watve (2013) proposed that the primary target of glucose homeostasis is

265 to regulate glucose levels in the brain. Plasma glucose levels are only a means to achieve the

266 required supply of glucose to the brain. Since the transport of glucose to the brain is more

267 restricted, when an adequate supply of glucose to the brain is ensured, it is likely that the

268 supply to other organs is already ensured.

269 In the Gaohua and Kimura (2009), as well as in the Watve (2013) model, the rate of glucose

270 transport across the BBB is assumed to be an adaptation to hyperglycemia. The finding that

271 glucose transport is reduced to an intermediate level in obese and prediabetic individuals

272 (Büsing et al., 2013; Hwang et al., 2017) suggests that the deficiency in transport precedes

273 hyperglycemia rather than following it. Therefore, it is more likely to be causal than

274 consequential. Glucose deficiency in the brain is known to induce liver glucose production

275 and suppress insulin release through autonomic control (Boland et al., 2017). Sympathetic

276 tone has also been shown to be higher in T2DM (Thackeray et al., 2012). Therefore, glucose

277 deficiency in the brain owing to altered vascular function is likely to be primary, which

278 results in altered plasma glucose dynamics mediated by autonomic inputs. Our model

279 incorporates this possibility.

280 Impaired vascular function is known to be central to diabetic complications. The classical

281 thinking has been that hyperglycemia causes the types of vasculopathies typical of T2DM.

282 However, it has not been ruled out that vasculopathies are not primary. There is

283 considerable evidence that microvascular alterations precede T2DM and are good

284 predictors of it (Muris et al., 2012; Nguyen et al., 2007; Stehouwer, 2018; Zaleska-Żmijewska

285 et al., 2017). A sedentary lifestyle and deficiency of many specific types of physical activities

286 and behaviours alter the expression of growth factors and endocrine mechanisms involved

287 in angiogenesis (Watve 2013). It has been demonstrated repeatedly that many growth

288 factors and angiogenic factors are responsive to behaviours, physical activity and exercise

289 (Aloe et al., 1994; Cao et al., 2010; Chodari et al., 2016; Lakshmanan, 1986; Nexø et al.,

290 1984; NEXØ et al., 1981; Tirassa et al., 2003). A deficiency of these behaviours is likely to

291 lead to a primary deficiency of angiogenic mechanisms (Watve, 2013). We consider the

292 possibility that altered vascular function in the brain is the primary reason why glucose

293 transport from blood to the brain is reduced. This creates chronic glucose deficiency in the

294 brain, to which the brain reacts by influencing multiple mechanisms of glucose regulation.

295 The predominant mechanism is autonomic signalling. It is well known that sympathetic and

296 parasympathetic tones are altered in T2DM (Thackeray et al., 2012). We consider the

297 possibility that altered autonomic signalling is causal rather than consequential to diabetes

298 based on studies showing that changes in autonomic function precede T2DM (Carnethon et

299 al., 2003).

300 The brain glucose uptake is insulin-independent (Gray et al., 2014; Hasselbalch et al., 1999).

301 Nevertheless, insulin has many other functions in the brain and insulin signalling is known to

302 be important in memory, cognition, decision making and behaviour (Kerns, 2001; Shemesh

303 et al., 2012; Strachan, 2003). The brain is rich in insulin receptors, and activation of certain

304 cognitive functions in the brain is a likely cause of increased brain glucose utilization by

305 insulin stimulation (Bingham et al., 2002; Rebelos et al., 2021). We assume, therefore, that

306 the brain has a fundamental requirement for insulin, independent of glucose metabolism

307 and therefore, mechanisms to ensure the required insulin levels in the brain are as critical as

308 ensuring minimum brain-glucose level. This is also ensured by autonomic mechanisms.

309 Autonomic inputs are known to regulate β cell population as well as insulin release from β

310 cells (Thorens, 2015). Therefore, our model also incorporates brain control over insulin

311 production.

312 Ensuring a minimum supply of glucose as well as insulin to the brain is crucial during fasting

313 when the plasma levels are low. The post-meal levels of glucose and insulin in the plasma

314 are much higher, and at this time, the brain need not actively regulate the plasma levels of

315 both. This can be taken care of by the peripheral mechanisms.

316   1.4 <u>Objectives of the model</u>**:**

317   Our attempt is to construct a model whose predicted outcomes match with all or most of

318   the observed phenomena listed above qualitatively. We intend to construct a model in

319   which different hypotheses for hyperglycemia can be used to make differential testable

320   predictions. This approach can allow us to evaluate comparatively which causal factors,

321   individually or in combination, can give us the set of predictions that match the patterns

322   listed above.

323   Out of the parameters required for the model, only some have empirical estimates available

324   (table 1). In the absence of realistic estimates of all parameters, we do not intend to make a

325   model making quantitative predictions. When a sufficiently large number of parameters can

326   be optimized, it is not difficult to fit the data quantitatively. Therefore, we prefer qualitative

327   predictions over quantitative ones. We test whether the model is able to predict the pattern

328   observed empirically under some set of parameters. The ability to predict a given pattern is

329   not proof of the validity of the model, but the inability to predict an observed phenomenon

330   at any set of parameters in a realistic range is a strong reason to call the model either

331   inadequate or wrong. If an additional consideration compatible with the model is able to

332   explain a pattern not explained by the main model, the model can be called inadequate but

333   not falsified. However, if the model outcome directly contradicts a consistent and

334   reproducible empirical finding, it can be considered falsifying evidence. We emphasize the

335   need to evaluate our model in comparison with classical models on these lines.

336   **2. Methods**

337   2.1 <u>Assumptions of the model</u>**:**

338   A unique assumption of our model based on the analysis by Diwekar-Joshi and Watve(2020)

339   is that the mechanism of regulation of glucose and insulin is different in the steady state and

340   post-meal state. In the steady state, the central mechanisms are more important, whereas,

341   in the post-meal state, mainly the peripheral mechanisms are at work. Insulin-induced

342   glucose uptake and insulin-dependent inhibition of liver glucose production happen only

343   above a threshold glucose and insulin level, respectively. The presence of such thresholds

344   and their context-dependent variability has been known for a long time (Chen et al., 1993;

345   Henquin et al., 2006; Sorensen, 1985). Below the threshold, other mechanisms regulate the

346   levels (Sorensen 1985). We assume in the model that the thresholds are under

347   neuroendocrine control and fine-tuned by the brain. The thresholds found in isolated cell

348   cultures are slightly lower than the normal fasting blood sugar, and it is difficult to estimate

349   thresholds in vivo (Chen et al., 1993; Henquin et al., 2006, 2015). In the presence of

350   autonomic signals, we assume the thresholds to be above the steady-state target levels. In

351   conditions under which the fasting levels need to increase, we assume the thresholds to

352   increase proportionately. This may happen with peripheral or central mechanisms. These

353   assumptions about the threshold make the model a TSS model.

354   The steady-state glucose is decided by a balance between the basal level of liver glucose

355   production, which is regulated by neuronal mechanisms and insulin-independent glucose

356   uptake by tissues. The steady-state insulin level is decided by the basal rate of glucose

357   independent insulin production, which is regulated by neuronal mechanisms against the

358   insulin degradation rate. Glucose is transported from plasma to the brain by facilitated

359   diffusion proportionate to capillary surface area in the brain and glut-1 expression. Steady-

360   state brain glucose is determined by glucose transport to the brain and utilization by brain

361   tissue. The brain needs a target level of glucose, and the brain ensures it by directly

362   regulating liver glucose production by neuronal mechanisms.

363   Insulin has cognitive and other functions in the brain (Begg & Woods, 2013; Kern et al.,

364   2001; Rohner-Jeanrenaud & Jeanrenaud, 1983; Shemesh et al., 2012; M W J Strachan,

365   2005), for which the brain requires a target level of insulin, which it ensures by autonomic

366   regulation of β cell number and basal insulin secretion independent of glucose. To ensure

367   the brain's target level for insulin, a minimum plasma insulin level needs to be maintained.

368   Maintenance of this level is assumed to be independent of glucose-stimulated insulin

369   secretion.

370   The rate of transport of glucose and insulin from blood to the brain is not constant. Both are

371   affected by the capillary density and blood flow. But they also depend upon specific

372   transport mechanisms. Glucose is transported across the blood-brain barrier mainly through

373   the specific transporter glut-1. The expression of glut-1 in the brain and other tissues is

374   variable and dependent on multiple dietary, endocrine and growth factor-related

375   mechanisms (Boado et al., 1994; Ge et al., 2011; Liu et al., 2018; Schüler et al., 2018).

376   Glucose transport from blood to the brain is diminished in obesity and prediabetes (Hwang

377   et al., 2017). Insulin transport to the brain is also reduced in obesity (Begg, 2015). The ratio

378   of CSF to plasma insulin is inversely proportionate to obesity and insulin resistance (Gray &

379   Barrett, 2018). Moreover, inducing endothelial dysfunction and reducing glucose transport

380   experimentally by endothelial-specific deletion of HIF 1-α resulted in hyperglycemia (Huang

381   et al. 2012). These findings validate our assumptions based on which we incorporate the

382   possibility of diminished glucose and insulin transport to the brain being the primary

383   pathology of T2DM and hyperglycemia only as a consequence.

384   **The model**:

385   Since we assume that the steady state and post-meal mechanisms of glucose regulations are

386   not identical, we model and analyze the two states in two phases of the model. The

387   variables and parameters used in the model and the range of parameters used are in Table

388   1.

s 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 the brain	Mg/dL/min	3 - 8
8	K_{8m}	Half saturation constant for glucose transport to the brain	mg/dL	50-100
9	K_9	Maximum rate of Insulin transport to the brain	µU/mL/min	0.6 - 1
10	K_{9m}	Half saturation constant for insulin transport to the 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*	The insulin threshold above which insulin-induced glucose disposal begins	μU/mL	2-5 μU/mL above *PI*

389

390

391

392

393

394

395

396

397

398

399

400

401

402

403

404

405

406

407

408

409

410

411

27	*PIT*	The insulin threshold above which insulin-induced glucose disposal begins	μU/mL	2-5 μU/mL above *PI*

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

413   A: Modeling steady-state glucose:

414   As per the assumption, below a threshold *PI*, insulin-induced glucose uptake and insulin-

415   induced inhibition of liver glucose production are negligible. Therefore, we write,

416   1. Plasma Glucose:

417
$$\frac{dPG}{dt} = \begin{cases} L - \frac{K_1 * PG}{K_{1m}+PG}, \ +Gt & (\underline{PI} < PIT) \\ L - \frac{K_1 * PG}{K_{1m}+PG} + Gt - \left(I_s * \frac{K_2 * PI}{K_{2m}+PI}\right) * PG, & (PI > PIT) \end{cases}$$
Eq. 1

418

419

420   2. Plasma Insulin:

421
$$\frac{dPI}{dt} = \begin{cases} K_4 - (d1 * PI), & (\underline{PG} < PGT) \\ K_4 - d1 * PI + \frac{K_5 * PG}{K_{5m}+PG} * (PG - PGT1), & (\underline{PG} > PGT) \end{cases}$$
Eq. 2

422   3. Brain glucose:

423
$$\frac{dBG}{dt} = \frac{K_8*(PG-BG)}{K_{8m}+(PG-BG)} - K_{10} * BG$$
Eq. 3

424   Since the brain forms only about 3 % of total body mass, we assume plasma glucose

425   diffused to the brain is a negligible fraction of total plasma glucose. Therefore, that term

426   is not included in the plasma glucose dynamics. Similarly, insulin diffusion to the brain

427   is not represented in the plasma insulin dynamics. Nevertheless, the rate of plasma to

428   brain diffusion is crucial in determining the brain glucose and insulin dynamics.

429   4. Brain insulin:

430
$$\frac{dBI}{dt} = \frac{K_9*(PI-BI)}{K_{9m}+(PI-BI)} - d_1 * BI$$
Eq. 4

431   At steady state (SS), all differential terms become zero, and steady-state levels can be

432   calculated using equilibrium solutions.

433   As per the assumption of the model, the brain needs a certain level of glucose, and that

434   is the target of homeostasis *BGt.* In order to ensure *BGt* at given K_8, K_{10} and K_{8m}, the SS

435   plasma glucose *PG* needs to be

436
$$\underline{PG} = \frac{BG_t * K_{10} * K_{8m}}{K_8 - (BGt * K_{10})} + BGt$$
Eq. 5

437 We assume that the brain ensures this plasma glucose level by regulating liver glucose

438 production L. To maintain the desired plasma glucose level at a steady state, the liver

439 glucose production should be:

440 $$L = \frac{K_1 * \underline{PG}}{K_{1m} + \underline{PG}}$$ Eq. 6

441 The brain can either ensure this by sending a calculated signal to the liver through the

442 autonomic system. Alternatively, this can be ensured by the brain by increasing

443 sympathetic inputs when $BG < BGt$ and parasympathetic when it is above target (Antuna-

444 Puente et al., 2009; D'Alessio et al., 2001; Kiba, 2004). The required L can be achieved

445 iteratively by $L_{(t+1)} = L_{(t)} + K_s.(BGt - BG)$

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

447 $$\underline{PI} = \frac{d_1 * BIt * K_{9m}}{K_9 - (d_1 * BIt)} + BIt$$ Eq. 7

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

449 $$K_4 = d_1.\underline{PI}$$ Eq. 8

450 Similar to glucose, the brain can ensure the target level of insulin in the brain by

451 neuronally modulating K_4 in a calculated or iterative manner. Specific autonomic inputs

452 are known to regulate β cell number as well as insulin release from β cells (Begg&

453 Woods, 2013; Boland et al., 2017; Kiba, 2004).

454 We also assume that both L and K_4 have a fixed upper limit as L_{max} and K_{4max} when the

455 maximum capacity of the liver and pancreas is reached. L and K_4 cannot exceed this

456 limit even if neuronal inputs become more intense. This happens when K_8 declines below

457 a threshold such that,

458 $$K_8 < \frac{K_1 - L_{max}(BGt * K_{10} * K_{8m})}{L_{max} * K_{1m} - BGt(K_1 - L_{max})} - (BGt * K_{10})$$ Eq. 9

459 There is a potential conflict here. Sympathetic tone is known to increase L (Nelles et al.,

460 1996; Nonogaki, 2000), whereas parasympathetic signal is required for proliferation of β

461 cells. Simultaneously, a sympathetic signal is known to inhibit insulin release from β cells

462 (Gilon & Henquin, 2001; Miller et al., 1976). If the brain is deficient in glucose as well as

463 insulin, both sympathetic and parasympathetic tones will be simultaneously higher (Watve

464   et al., 2014). This is incorporated into the model by updating K_4 iteratively according to both

465   *BG* and *BI* levels simultaneously,

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

467   By this consideration, if sympathetic stimulation of liver glucose production is adequate to

468   restore required *BG*, $BGt - BG$ will tend to zero, and there will be no interference in insulin

469   release by β cells. However, in case the rise in liver glucose production is inadequate to

470   ensure required *BG*, K_4 will be affected, which will apparently influence β cell function.

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

472   While for the steady state, equilibrium solutions can be algebraically derived, the post-

473   glucose load curve and its properties can only be obtained by simulations. Simulations were

474   run using the same set of equations and giving a positive ephemeral *Gt* to simulate food

475   intake.

476   In all the simulations used, insulin resistance can be simulated by altering *Is*, β cell

477   dysfunction by reducing *K_4* and/or *K_5* and vascular defect slowing down the transport of

478   glucose and insulin to the brain and other organs by altering *K_8*, *K_9* and *K_1*. Mental stress is

479   assumed to increase *K_{10}*. By differentially altering these parameters, the model can

480   separately and collectively examine the effects of insulin resistance, β cell dysfunction,

481   reduced rates of diffusion across BBB and stress on the glucose tolerance curve.

482

483   <u>T2DM- causal analysis</u>: We ask the question of which minimal set of changes can give rise to

484   a stable increase in fasting glucose, changes in the glucose tolerance curve characteristic of

485   type 2 diabetes, and other patterns listed above. The putative causal factors are examined

486   individually and in combination. The factors include insulin resistance (Decreased *I_s*),

487   subnormal β cell response (Reduced *K_4 and/or K_5*), reduced insulin-independent glucose

488   uptake (decrease in *K_1*), reduced blood-to-brain transmission of glucose (*K_8*) and insulin (*K_9*)

489   and stress-related increase in brain glucose consumption (*K_{10}*). Subnormal or defective

490   vasculature is expected to decrease *K_1, K_8* and *K_9* proportionately; however, the decrease in

491   the three parameters may not be proportionate if the vasculature in different parts of the

492   body is differentially affected. Also, glucose transporters and their expressions can alter in a

493   tissue-specific manner. Therefore, we allow proportionate as well as differential decrease in

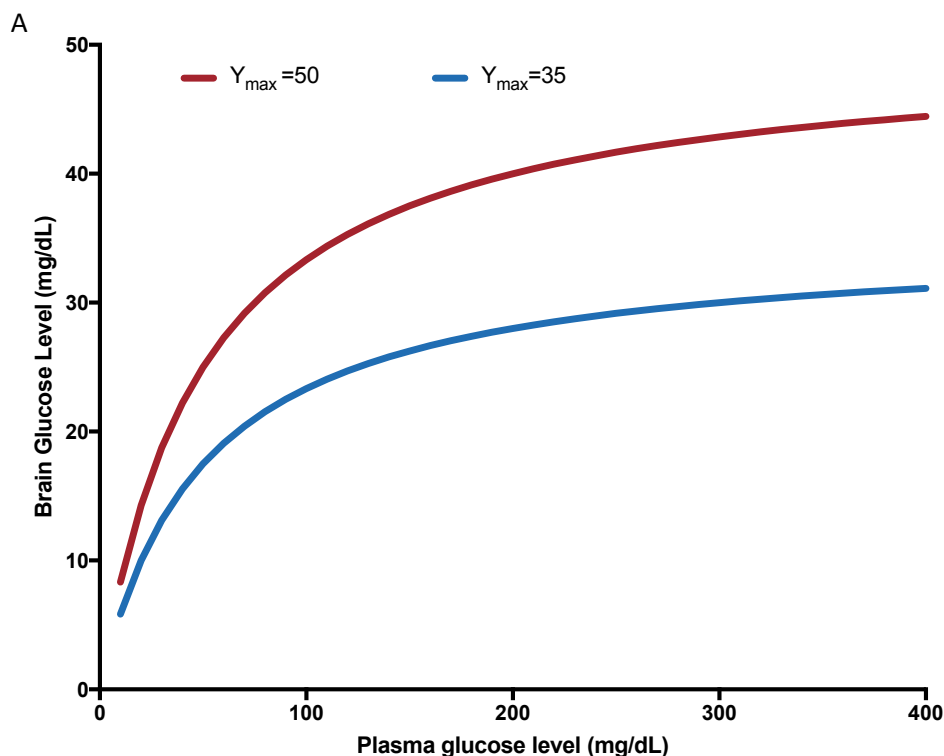494   the three parameters.

495   **Results**:

496   <u>A: Steady-state solutions</u>: We observed that the steady-state solutions and the autonomic

497   iteration simulations match well in the end result except when the limits of L and K_4 are

498   reached. However, it took a long time to reach the desired level by iterative approach,

499   particularly when the desired level was substantially different from the starting level. In real

500   life, major changes in vascular function or glucose transporter levels reflected in K_8, K_9, and

501   K_1 happen gradually. Therefore, the desired level can be attained by autonomic fine-tuning

502   over time. Since, in the iterative simulations, a long time was required to reach SS, we used

503   the steady-state solutions for quicker results.

504   It can be seen that the steady-state levels of PG in the model is a stable, steady state since

505   substituting PG <$\underline{PG}$ leads to a positive value and PG >$\underline{PG}$ leads to a negative value of $\frac{dPG}{dt}$.

506   The same applies to plasma insulin, brain glucose and brain insulin. This ensures a stable,

507   steady state of glucose-insulin in the plasma as well as in the brain on fasting [1,2]. From

508   equations 5,6, and 8, we see that FG does not change by altering Is or FI. This is compatible

509   with the empirical findings that insulin receptor knockouts and insulin suppression

510   experiments fail to increase fasting plasma glucose [9]. This result is unique to our model

511   and is due to segregating fasting and post-meal glucose regulation mechanisms by using

512   thresholds. This is the only explanation offered so far for patterns [9], [16] and [17].
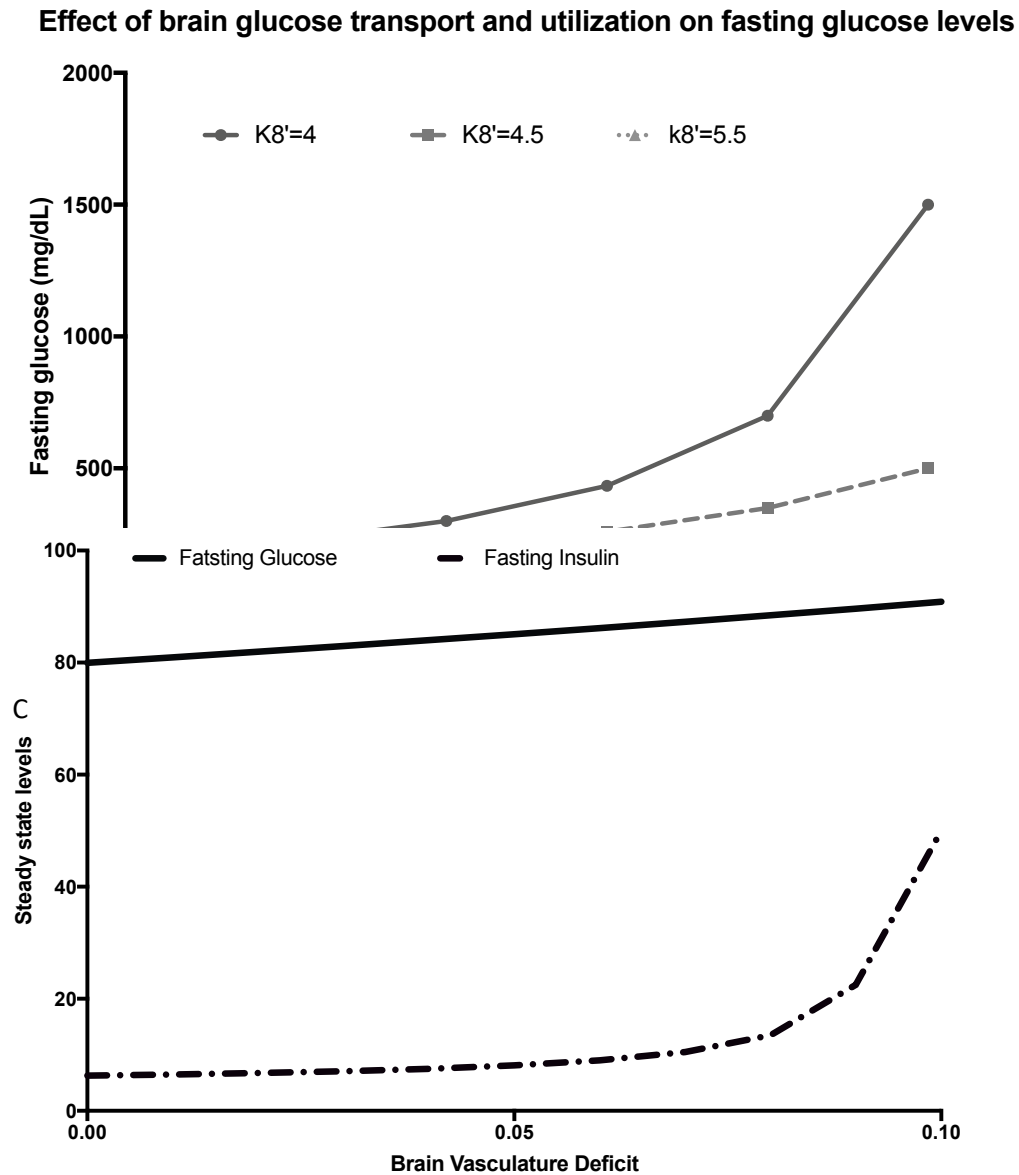
513   The steady-state solution of our model shows that FG can increase as a result of an increase

514   in K_{10} or a decrease in K_8. That is, if the glucose consumption in the brain increases and/or

515   the rate of glucose transport from blood to the brain decreases. Both the effects are

516   interdependent, and the shape of the glucose response is decided by the interaction

517   between K_8 and K_{10}. Increased K_{10} increases FG marginally and almost linearly when K_8 is

518   large. When K_8 decreases, even a marginal rise in K_{10} can induce a disproportionately

519   greater rise in FG (fig 1). This means that stress-induced hyperglycemia is unlikely to be seen

520   in healthy individuals, while it is more likely in individuals with reduced vascular transport

521   [7].

522   *Figure 1: The same input different output phenomenon:*

523   *A. A conceptual diagram with arbitrary units: A saturation relationship in glucose and*
524   *insulin transport described by a Michaelis Menten type of equation has important*
525   *consequences that can account for many phenomena observed in prediabetic and*
526   *diabetic stages. For example, here, for achieving an increase in Y by 6 units with a*
527   *higher Y_{max}, X needs to increase only by 6 units, but at a lower Y_{max} for the same*
528   *target increase in Y, 25 units of increment in X is needed. This non-linearity explains*
529   *many phenomena, including prediabetic hyperinsulinemia and stress-induced*
530   *diabetes in our model of glucose homeostasis.*
531   *B. A simulation using the steady state model: It can be seen that as K_8 decreases, for the*
532   *same change in brain requirement K_{10}, a non-linear escalated increase in plasma*
533   *glucose is required.*
534   *C. A simulation result assuming a correlated decrease in K_8 and K_9. It is possible that*
535   *while glucose shows a marginal increase, insulin increases substantially, since the*
536   *parameters of glucose and insulin transport curves are different. This is a potential*
537   *explanation for the hyperinsulinemic normoglycemic state.*

538

A

B

Effect of brain glucose transport and utilization on fasting glucose levels

539

540

541   The origin of the hyperinsulinemic normoglycemic condition can be explained by the

542   difference in the parameters of the saturation curves of transport dynamics of

543   glucose and insulin. If the insulin diffusion is assumed to be nearer to saturation and

544   glucose diffusion is sufficiently away from saturation, at the same level of vascular

545   function deficiency, insulin will increase disproportionately more than glucose

546   (Figure 1). This is a possible cause of hyperinsulinemic normoglycemic state [3] and

547   the reason why hyperinsulinemia precedes hyperglycemia [4], which requires neither

548   insulin resistance nor compensatory hyperinsulinemic response. When this happens,

549   both HOMA-IR and HOMA β increase, although there is no change in true insulin

550   resistance and compensatory insulin response. This gives a false impression of insulin

551   resistance as clinically defined.

552   Further, as the transport saturation constant K_8 and K_9 continue to decrease

553   proportionately, FG increases monotonically, but FI shows a non-monotonic curve in

554   which FI increases with a moderate decrease in transport rates but decreases after a

555   threshold decrease in transport rates. This non-monotonicity is predicted by the

556   iterative autonomic inputs model. When the required L approaches or exceeds L_{max},

557   the steady state BG remains smaller than BGt. The resultant increase in the

558   sympathetic signal inhibits insulin release from β cells. This leads to reduced insulin

559   secretion, and insulin levels drop substantially. Thus, without bringing in additional

560   factors, the model explains the early phase rise in fasting insulin as well as the later

561   phase decline in the course of T2DM [4] (Figure 2).

Effect of decrease in glucose and insulin transport to brain

562
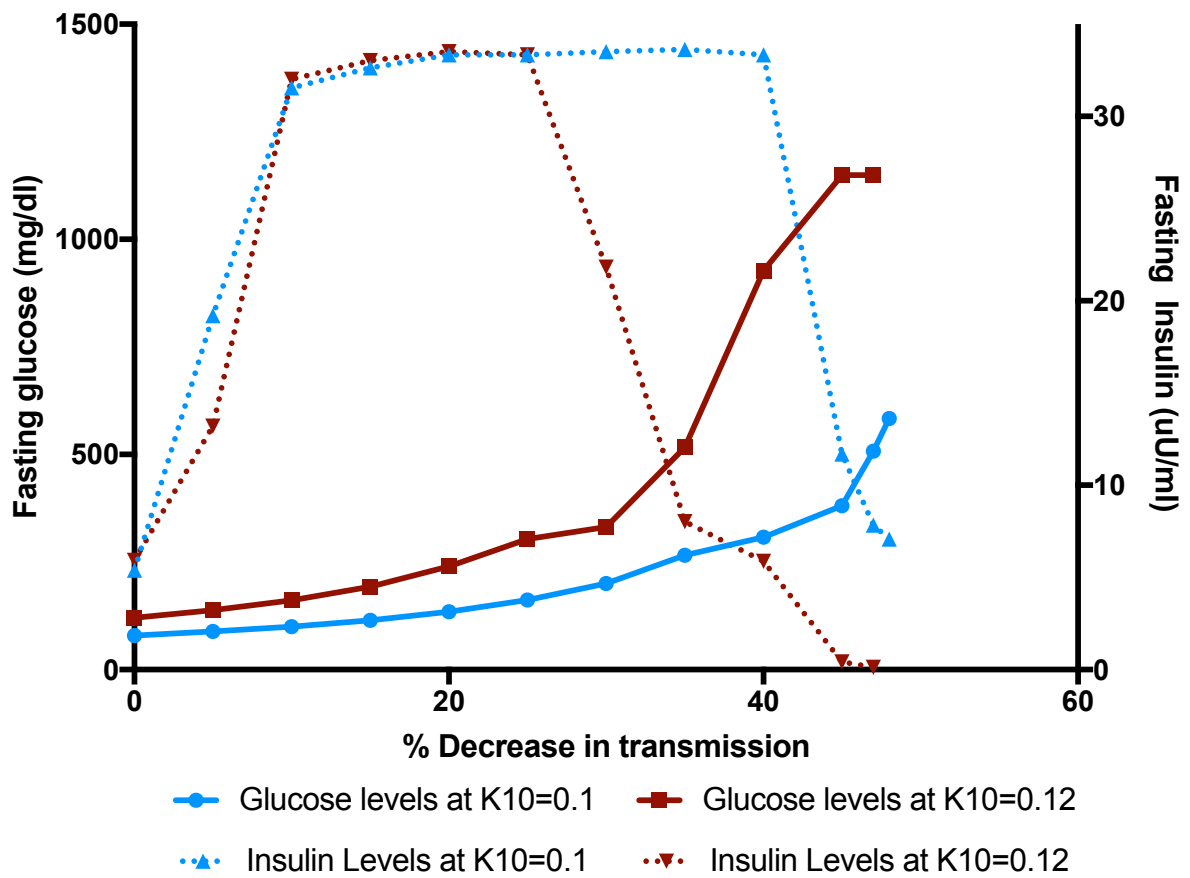
563   *Figure 2: Effect of correlated decrease in K_8 and K_9 on fasting plasma glucose and insulin.*

564   *Note that for a small to moderate decrease, FI increases rapidly with marginal change in FG.*

565 *However, after a threshold decrease in the transport rates, FI declines sharply, whereas FG*

566 *increases rapidly. This pattern matches with the course of clinical T2DM without involving*

567 *insulin resistance, compensatory hyperinsulinemia and β cell exhaustion. Simulation-specific*

568 *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,*

569 *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).*

570 This decline in the insulin response does not require β cell dysfunction as a causal

571 mechanism, but there are more complex possible effects on β cells. Simultaneous activation

572 of sympathetic and parasympathetic inputs to β cells is implicated in β cell amyloidogenesis

573 (Watve et al., 2014). Parasympathetic stimulation is known to increase β cell number.

574 However, sympathetic signalling suppresses insulin release resulting in increased retention

575 time of insulin along with amylin which, beyond threshold retardation, may result in

576 spontaneous polymerization of amyloid protein leading to poisoning of β cells and

577 amyloidogenesis (Watve et al., 2014). This is an alternative causal interpretation of β cell

578 dysfunction and decline in its population. This mechanism has a built-in negative feedback

579 loop, giving rise to a steady-state β cell population. This result is compatible with the finding

580 that the β cell population remains subnormal lifelong [11,12]. This is in contrast with the

581 dynamics expected by classical thinking in which β cells are destroyed by gluco-lipotoxicity

582 or oxidative stress. This mechanism has a built-in positive feedback cycle. As a part of the β

583 cell population is destroyed, insulin secretion is decreased, which would increase glucose,

584 further accelerating gluco-lipotoxicity and oxidative stress and thereby β cell loss. Such a

585 positive feedback vicious cycle can only stop with the complete destruction of the β cell

586 population. This prediction of the classical model does not match the finding of sustained

587 presence of subnormal β cell population in T2DM.

588 By the classical model, prolonged sustained exercise in the fasting state should result in

589 lower plasma glucose. However, an experimental increase in glucose uptake resulting from

590 physical activity during fasting does not necessarily result in a decrease in *FG*. This is mainly

591 because as *FG* starts decreasing, *BG* decreases consequently. *BG* being lower than *BGt*

592 induces a sympathetic-mediated increase in *L,* and the change in *FG* by physical activity is

593 more or less compensated. This may happen through the agency of glucagon as well since a

594 strong link between autonomic signals and glucagon secretion is known. Therefore, at times,

595 plasma glucose may actually increase after intensive exercise. Further, if exercise involves

596   heightened activation of cerebellar mechanisms of coordination, K_{10} may also increase,

597   resulting in higher rather than lower *FG* in response to exercise [8].

598   A high dose of exogenous insulin results in increased plasma glucose after a time lag, which

599   is known as the Somogyi phenomenon. The phenomenon is conditional and not seen in

600   every diabetic. It is said to involve the counter-regulatory response to facing central

601   hypoglycorrhachia. However, often, this response is seen without peripheral hypoglycemia.

602   This is best explained by reduced K_8, which gives rise to a decreased *BG/FG* ratio. With

603   smaller K_8, at apparently normal or increased plasma glucose, brain glucose can still be

604   lower than the target, which gives a sympathetic signal to increase *L*. Simulations using the

605   autonomic iteration model show this phenomenon quite well at low K_8. At the same level of

606   insulin infusion, at lower K_8 there is a more intense hyperglycemic response (Figure 3) [14].

607   A model without accommodating changes in K_8 does not predict the Somogyi phenomenon

608   without an obvious hypoglycemic state.

609   At transportation rate 90%

610
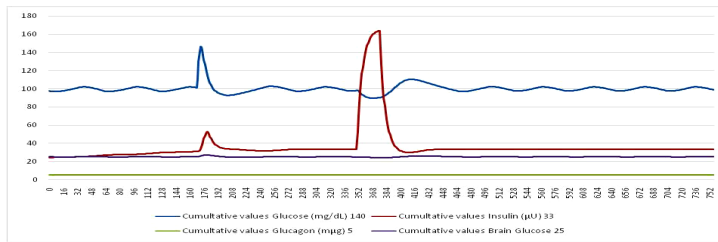
611   At transportation rate 70%

612
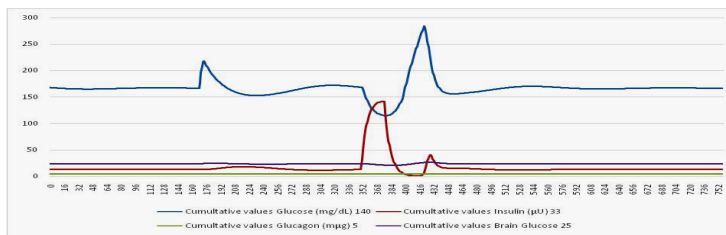
613   *Figure 3: Effect of high-dose insulin on peripheral glucose under two rates of glucose and*

614   *insulin transport across the blood-brain barrier (Correlated decrease in K_8 and K_9). A*

615   *paradoxical rise in blood sugar following insulin administration is more prominent when the*

616   *transport rate is substantially lower than normal. Other parameters (K_{1m} =50, K_1=30, K_{2m}=15,*

617   *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,*

618   *K_{10}=0.1)*

619   The response is restricted to a narrow set of conditions. For intense hyperglycemic response

620   to insulin administration, it is necessary that insulin sensitivity is good, BG is close to BGt

621   before insulin transfusion, and K_8 is subnormal.

622   Potentially, one can visualize two distinct possible classes of reasons why blood sugar

623   increases in response to brain injury. In the first, there is some impairment in the glucose

624   regulation mechanism. In the second, the requirement for glucose is increased during the

625   wound healing process, and hyperglycemia is a mechanism of the body to meet the

626   demand. It is known that infections such as meningitis, stroke or haemorrhage lead to

627   transient hyperglycemia. Such hyperglycemia is often accompanied by lower BG levels

628   (Schut et al., 2009; van Veen et al., 2016)[15]. In such cases, hypoglycemic treatments can

629   be counterproductive and result in a delayed or derailed repair process. This is a likely

630   reason why, in patients under intensive care, strict regulation of plasma glucose increases

631   mortality instead of the expected decrease (The NICE-SUGAR Study Investigators, 2009).

632   When hyperglycemia is a process of meeting increased glucose demand or compensating

633   subnormal transport, the removal of plasma glucose by any means is expected to increase L.

634   This is observed to happen when SGLT2 inhibitors decrease the urinary threshold and drive

635   out plasma glucose. If increasing L is not sufficient to restore the required glucose level,

636   there is a shift to ketogenesis since the brain can use keto acids as an alternative source of

637   energy. Therefore, increased L with or without increased ketogenesis is expected by our

638   model following SGLT2 inhibitors [13].

639   B: Glucose tolerance curve: Unlike the steady-state predictions, the patterns of the post-

640   feeding glucose curve by our model are not qualitatively different from classical models. The

641   area under the curve, the height of the peak, the time required to return to a steady state

642   and the time difference between glucose and insulin peaks are increased by decreased I_s, K_5,

643   or K_8 individually or in combination. Decrease in I_s or K_5 does not increase FG but changes

644   the shape of the glucose tolerance curve. Decreased K_8 may alter both simultaneously. The

645   altered curve shows the three typical features, namely a taller peak, delayed return to a

646   steady state and a longer gap between glucose peak and insulin peak [5]. This result is not

647   unique to our model, and classical models also show the three features. The classical model

648   results in simultaneous and proportionate alterations in the fasting as well as post-meal

649   glucose and, therefore, fails to explain the NFG-IGT state. In our model, decreasing I_s or K_1

650   without a change in K_8 results in an NFG-IGT state [6].

651

652   <u>C: Population simulations</u>: For the steady state as well as post-glucose load dynamics, we

653   give population distributions to K_1, K_5, K_8, K_9, I_s and also incorporate normally distributed

654   error in glucose and insulin measurements in fasting and post-meal sampling. We also

655   incorporate correlated changes in K_1, K_8 and K_9, which are expected as a result of hypo-

656   vascularization in the brain. These simulations are run to observe whether we get the

657   anomalous correlations in fasting versus post-meal state and in the HOMA indices as

658   observed empirically (Chawla et al., 2018; Diwekar-Joshi & Watve, 2020).

659   By classical models, the regression correlation parameters of the glucose-insulin relationship

660   are not different in the fasting state versus post-glucose load, although the range of

661   variables is different, as shown previously by Diwekar-Joshi and Watve (2020). Also, if we

662   assume HOMA-IR to faithfully reflect insulin resistance and HOMA β to faithfully represent β

663   cell response, then there is no reason why the two indices should be correlated.

664   The assumption behind our model that there are different mechanisms at work under

665   fasting versus post-glucose load conditions is necessary to explain the large difference in the

666   regression correlation parameters in fasting versus post-meal levels. If the same set of

667   mechanisms in the fasting and post-meal conditions are operational, whatever the model

668   used, it is imperative that fasting correlation regression parameters are stronger or

669   comparable to post-meal parameters. Simulations with our model are able to give poor *FG-*

670   *FI* correlation along with strong post-meal glucose insulin correlation under multiple

671   conditions [16] (Figure 4). When the variance in K_8 and K_9 is small but that in K_1, K_5, Gt and I_s

672   individually or in combination is large, the fasting correlations are weak and post-meal

673   correlations strong; the post-meal glucose-insulin regression slope is substantially greater

674   than *FG-FI* slope. Also, whenever the *FG-FI* correlation is weak, the indices HOMA-IR and

675   HOMA β are strongly correlated, similar to the epidemiological data [17]. The difference

676   between fasting and post-meal regression correlation patterns is not predicted by the

677   classical models and is unique to our model, which assumes a different set of regulatory

678   mechanisms in the fasting and post-meal state.
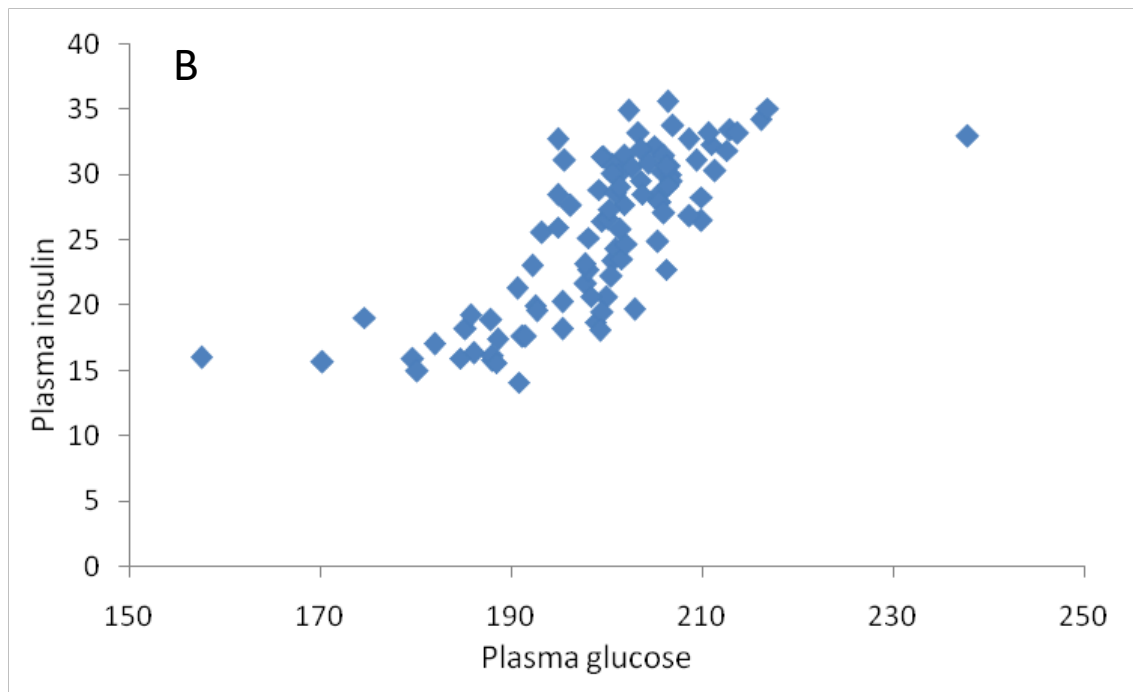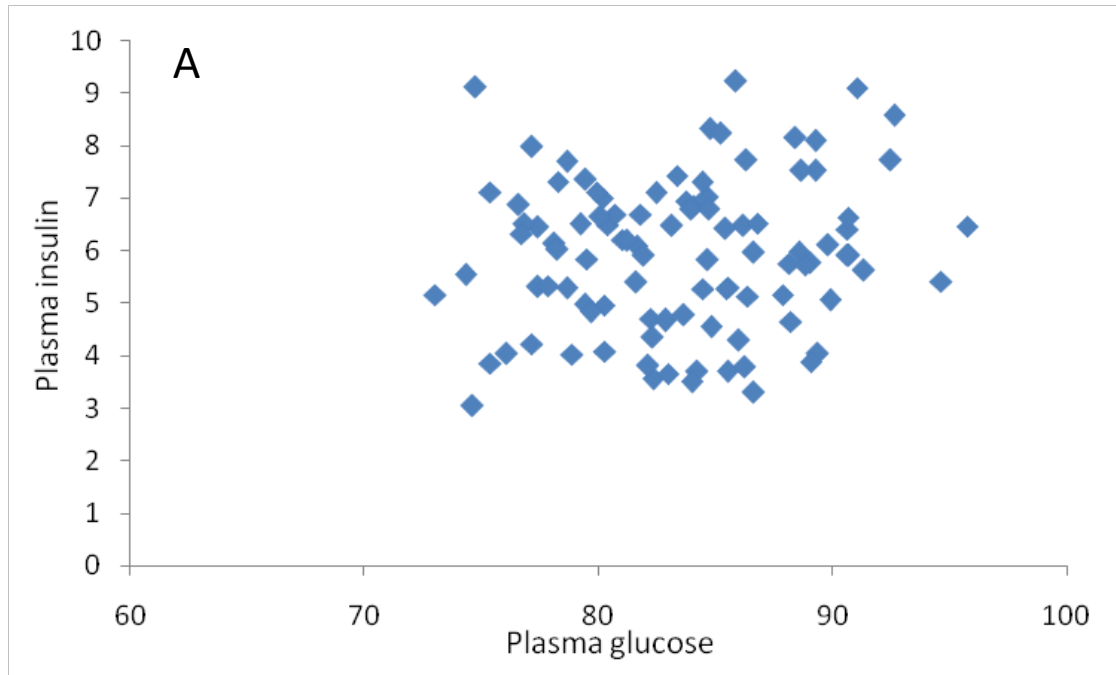
679

680

681   *Figure 4: Plasma glucose and insulin correlation in the fasting steady state (A) and post-meal*

682   *(B) in simulations. The empirical finding that there is a strong positive correlation in the post-*

683   *meal data but poor correlation in fasting steady state was possible under a variety of*

684   *conditions in our model. Depicted here are the simulation results (post-meal R^2=0.57, steady*

685   *state R^2=0.014) in which only K_1 was given a wider population distribution. (mean (S.D.) K_1 =*

686   *35(7), K_5 = 10(0.00001), K_8 = 5(0.000005), and K_9 = 0.8(0.000008). Other parameters (K_{1m}*

687   *=50, K_{2m}=15, K_2=0.05, d_1=0.15, I_s=1, BGt=25, BI=4.5, K_{8m}=80, K_{10}=0.1).*

688   D: Effect of glucose normalization on arresting diabetic complications and mortality: By

689   classical thinking, chronic hyperglycemia is responsible for diabetic complications and

690   preventing hyperglycemia should arrest complications. In contrast, the thought behind our

691   model is that vascular problems are primary, which alter the rate of glucose-insulin

692   transport to the brain, and hyperglycemia is an offshoot symptom that may not be causal to

693   diabetic complications. Diabetic complications can arise directly from the vasculopathy.

694   Therefore, controlling glucose may not have any effect on diabetic complications [18]. On

695   the other hand, forcefully reducing plasma sugar without addressing vascular problems can

696   create more severe glucose deficiency in the brain and other organs, thereby turning

697   counterproductive. Because of the saturating dynamics of transport, a curvilinear

698   relationship is expected between plasma glucose and brain glucose in such a way that a

699   moderate reduction in hyperglycemia will change brain glucose availability marginally,

700   whereas tight glucose regulation can have a disproportionately larger effect (Figure 5).

701   Therefore, tight glucose regulation may increase mortality and other adverse outcomes.

702   This prediction is compatible with some of the tight versus moderate control clinical trials,

703   including ACCORD, NICE sugar trial and UGDP [18].

704
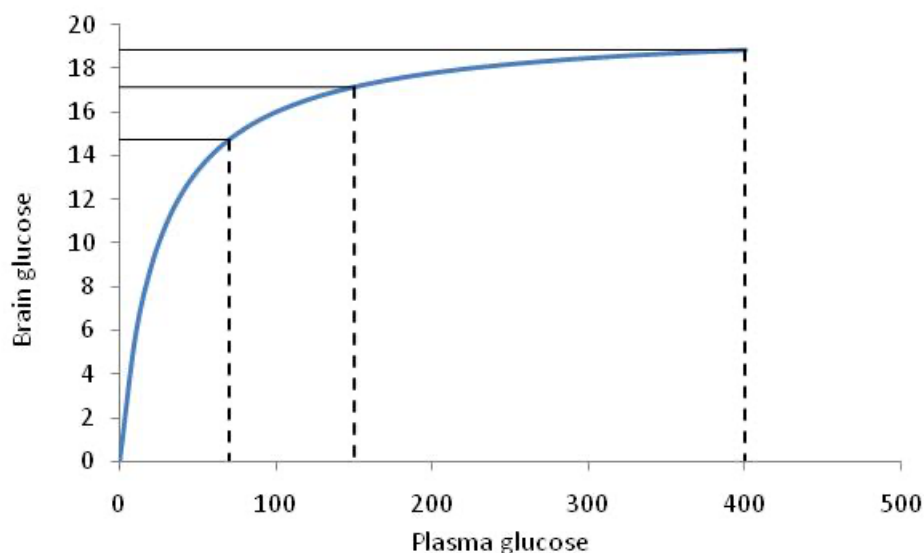
705   *Figure 5: Effect of glucose lowering on brain glucose availability. For example, a reduction in*

706   *FG from 400 mg/dl to 150 mg/dl corresponds to a decrease in BG by 1.68 mg/dl, but further*

707   *reduction from 150 to 70 mg/dl reduces BG by 2.41 mg/dl. Therefore, moderate sugar*

708   *control may not affect brain glucose supply drastically, but tight sugar control is expected to*

709   *affect it more seriously.*

710 **Discussion**:

711 The main inference from our model, stated most conservatively, is that a brain-centred

712 model can potentially explain most of the anomalies faced by peripheral models and,

713 therefore, needs greater attention (Figure 6). If supported well, by exploring its testable

714 predictions suggested below and possibly more, it has the potential to bring in a radical

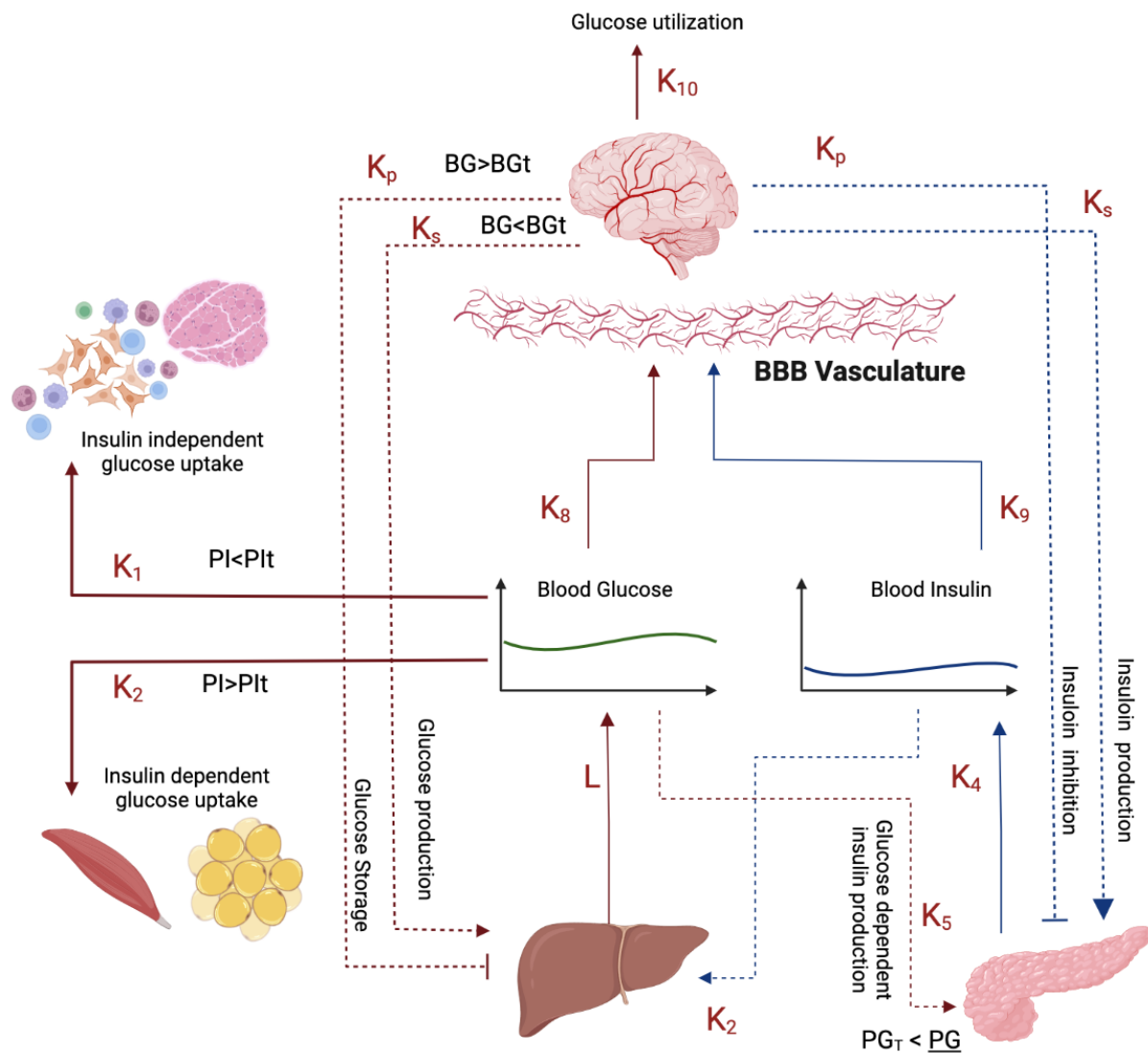715 change in the fundamental view as well as the clinical practice of T2DM.

716

717 *Figure 6: Effect of changes in vasculature in the brain barrier. The model predicts that glucose and*

718 *insulin transportation to the brain has a major role in the development of diabetic symptoms*

719 *compared to other peripheral changes. The blood-brain barrier vasculature, hence, may hold the key*

720 *to understanding the shift from normal to diabetic condition. (created using BioRender)*

721 Testability of assumptions and additional predictions:

722   The assumption that the thresholds *PGT* and *PIT* can be modified by autonomous signalling

723   needs to be tested empirically. Although, currently, the thresholds are known to be flexible,

724   information about the conditions and mechanisms of change is poorly known. Our

725   assumption is that the parameters of the saturation equation for glucose and insulin

726   transport to the brain are different and, under normal conditions, insulin transport is closer

727   to saturation than glucose transport can be tested with carefully worked out kinetics of the

728   two transport mechanisms.

729   The assumption of our model that reduced transport of glucose and insulin to the brain is

730   the primary pathology of T2DM leading secondarily to hyperglycemia makes more

731   predictions that can be tested experimentally or epidemiologically. Experimentally,

732   specifically blocking glut1 receptors in the brain should lead to hyperglycemia. Conversely,

733   the infusion of glucose directly into the brain should reduce peripheral hyperglycemia in the

734   short run. This is already suggested by some experiments (Ono et al., 1983; Osundiji et al.,

735   2012). It is also demonstrated that inducing primary endothelial dysfunction and reduced

736   glucose transport to the brain by endothelial deletion of hypoxia-inducible factor HIF-1α

737   results in hyperglycemia (Huang et al., 2012). More careful research in this direction to

738   reveal the cause-effect relationship between vascular defects, brain glucose levels, and

739   plasma glucose levels will be enlightening. Epidemiologically, hypoglycemia is shown to

740   associate with dementia and other neuronal problems (Lipska & Montori, 2013; Meneilly &

741   Tessier, 2016; Rhee, 2017; Yaffe, 2013), tight glycemic control led to higher mortality as

742   compared to moderate control in many of the clinical trials (Klein, 2010; Schwartz &

743   Meinert, 2004; The NICE-SUGAR Study Investigators, 2009) which demands investigations

744   into the causal pathways. The question of whether tight glycemic control leads to subtle

745   neuronal changes in the long run, as expected by our model, needs careful investigation.

746   The difference between fasting and post-meal regression correlation parameters between

747   glucose and insulin is an important epidemiological line of evidence we have used. Chawla

748   et al. (2017) and Diwekar-Joshi and Watve (2020) showed this pattern across four different

749   data sets. How generalized the pattern is needs to be tested in multiple population studies.

750   On the modelling front, it is necessary to undertake a comparative evaluation of the

751   different models with respect to the battery of predictions that we listed here. Perhaps a

752   few more predictions may be added. However, at present, many of the models and their

753 possible modifications are not explored sufficiently to see whether they can explain the

754 currently unexplained patterns under certain sets of conditions. A model prediction matrix

755 would be an appropriate approach for such a comparative evaluation, but we may have to

756 wait till all alternative models are explored sufficiently elaborately on which of the empirical

757 patterns they predict, which ones they are compatible with and which ones they contradict.

758 We have shown here that the brain-centred model predicts or is compatible with all the

759 patterns listed in the introduction and does not contradict any.

760 <u>Possible causes of T2DM:</u>

761 The classically believed causal factors, namely insulin resistance and β cell dysfunction, are

762 not compatible with many of the empirical findings, as shown by Diwekar-Joshi and Watve

763 (2020). In our model, changes in insulin resistance and β cell dysfunction were neither

764 necessary nor sufficient to account for all the patterns. Nevertheless, they were helpful in

765 accounting for the altered glucose tolerance curve, although other factors could also

766 account for it independent of insulin resistance. Incorporating insulin resistance in our

767 model and assuming it to work only in the post-feeding state, patterns 1,2,5,6,9,16 and 17

768 could be explained but not others. In short, our model does not rule out insulin resistance as

769 a phenomenon but implies that it may not be central to T2DM. Primary vasculature

770 impairment reducing glucose and insulin transport in a mutually correlated or uncorrelated

771 manner could explain all patterns and, therefore, makes the most parsimonious causal

772 hypothesis. Particularly, assuming that altered vascular function affects K_1 early, followed by

773 K_8 and K_9, is sufficient to explain all the patterns without alteration in I_s or any other factor.

774 The apparent β cell dysfunction is an inevitable effect of a higher degree of vascular

775 dysfunction and altered autonomic signals and, therefore, may not be needed as an

776 independent causal factor.

777 Being open to alternative possibilities is an important virtue of science, and it is particularly

778 important with the limited clinical success of prevalent thinking along with mounting

779 anomalous findings. Prevention of T2DM on a global scale has largely failed, and treatment

780 has limited and inconsistent success in arresting mortality and morbidities associated with

781 T2DM (Brown et al., 2004; DeFronzo, 2010; Rosengren et al., 2008; Lee et al., 2021).

782 Therefore, exploring alternative possible interpretations is a need of the time.

783   Triggered by multiple anomalies in the theory of glucose homeostasis and the origins of

784   diabetic hyperglycemia, we have articulated here an alternative paradigm which potentially

785   resolves in a logically and mathematically consistent manner many of the anomalous

786   findings. Being mathematically and logically sound and compatible with evidence is not

787   sufficient proof of a theory but certainly reflects its potential to develop into a new

788   alternative paradigm. For a large field such as T2DM, multiple efforts would be needed to

789   evaluate competing paradigms. We have suggested a few more testable predictions that can

790   help in this task. There can be more possible ways of testing them, which should come to

791   light and be used to reach robust conclusions which have the potential to change the clinical

792   course of prevention as well as treatment of an important global health problem.

793   If our proposed causal inference that vascular dysfunction is primary to T2DM is necessary

794   and might even be sufficient to lead to all the observed symptoms and patterns is supported

795   by more careful investigations, it explains the failure of glucose normalizing treatment in

796   arresting diabetic complications. Simultaneously, it suggests alternative lines of treatments

797   which should focus on normalizing vascular and neuronal function rather than focusing on

798   glucose normalization. The deficiencies of stimuli normally required for growth factors and

799   other angiogenic and neuroprotective factors can be forecasted as the best bet for the new

800   approach. However, rigorous efforts are needed to strengthen the evidence base for

801   selecting the right one amongst the alternative paradigms.

802

803   **References:**

804   Ajmera, I., Swat, M., Laibe, C., Le Novère, N., & Chelliah, V. (2013). The impact of

805   mathematical modeling on the understanding of diabetes and related complications.

806   *CPT: Pharmacometrics & Systems Pharmacology*, *2*(7), 54.

807   https://doi.org/10.1038/psp.2013.30

808   Aloe, L., Bracci-Laudiero, L., Alleva, E., Lambiase, A., Micera, A., & Tirassa, P. (1994).

809   Emotional stress induced by parachute jumping enhances blood nerve growth factor

810   levels and the distribution of nerve growth factor receptors in lymphocytes.

811   *Proceedings of the National Academy of Sciences*, *91*(22), 10440–10444.

812   https://doi.org/10.1073/pnas.91.22.10440

813 Antuna-Puente, B., Disse, E., Lavoie, M.-E., Rabasa-Lhoret, R., Laville, M., & Bastard, J.-P.
814   (2009). Evaluation of the SIisOGTT index in a healthy population with normal glucose
815   tolerance. *Diabetes & Metabolism*, *35*(3), 236–237.
816   https://doi.org/10.1016/j.diabet.2009.02.004

817 Bacha, F., Gungor, N., Lee, S., & Arslanian, S. A. (2013). Progressive deterioration of β-cell
818   function in obese youth with type 2 diabetes. *Pediatric Diabetes*, *14*(2), 106–111.
819   https://doi.org/10.1111/j.1399-5448.2012.00915.x

820 Banting, F. G., Best, C. H., Collip, J. B., Campbell, W. R., & Fletcher, A. A. (1922). Pancreatic
821   Extracts in the Treatment of Diabetes Mellitus. *Canadian Medical Association Journal*,
822   *12*(3), 141–146. https://www.ncbi.nlm.nih.gov/pubmed/20314060

823 Begg, D. P. (2015). *Insulin Transport into the Brain and Cerebrospinal Fluid* (pp. 229–248).
824   https://doi.org/10.1016/bs.vh.2014.12.007

825 Begg, D. P., & Woods, S. C. (2013). Interactions between the central nervous system and
826   pancreatic islet secretions: a historical perspective. *Advances in Physiology Education*,
827   *37*(1), 53–60. https://doi.org/10.1152/advan.00167.2012

828 Bernard, C. (1859). *Leçons sur les phénomènes de la vie. Cours de physiologies generale du
829   Museum d'Histoir Naturelle*. Paris: Librairie Delagrave.

830 Bingham, E. M., Hopkins, D., Smith, D., Pernet, A., Hallett, W., Reed, L., Marsden, P. K., &
831   Amiel, S. A. (2002). The Role of Insulin in Human Brain Glucose Metabolism. *Diabetes*,
832   *51*(12), 3384–3390. https://doi.org/10.2337/diabetes.51.12.3384

833 Blüher, M., Michael, M. D., Peroni, O. D., Ueki, K., Carter, N., Kahn, B. B., & Kahn, C. R.
834   (2002). Adipose tissue selective insulin receptor knockout protects against obesity and
835   obesity-related glucose intolerance. *Developmental Cell*, *3*(1), 25–38.
836   https://doi.org/10.1016/S1534-5807(02)00199-5

837 Boado, R. J., Black, K. L., & Pardridge, W. M. (1994). Gene expression of GLUT3 and GLUT1
838   glucose transporters in human brain tumors. *Molecular Brain Research*, *27*(1), 51–57.
839   https://doi.org/10.1016/0169-328X(94)90183-X

840 Boland, B. B., Rhodes, C. J., & Grimsby, J. S. (2017). The dynamic plasticity of insulin

841   production in β-cells. *Molecular Metabolism*, *6*(9), 958–973.

842   https://doi.org/10.1016/j.molmet.2017.04.010

843   Brown, J. B., Nichols, G. A., & Perry, A. (2004). The Burden of Treatment Failure in Type 2

844   Diabetes. *Diabetes Care*, *27*(7), 1535–1540. https://doi.org/10.2337/diacare.27.7.1535

845   Büsing, K. A., Schönberg, S. O., Brade, J., & Wasser, K. (2013). Impact of blood glucose,

846   diabetes, insulin, and obesity on standardized uptake values in tumors and healthy

847   organs on 18F-FDG PET/CT. *Nuclear Medicine and Biology*, *40*(2), 206–213.

848   https://doi.org/10.1016/j.nucmedbio.2012.10.014

849   Butler, A. E., Janson, J., Bonner-Weir, S., Ritzel, R., Rizza, R. A., & Butler, P. C. (2003). -Cell

850   Deficit and Increased -Cell Apoptosis in Humans With Type 2 Diabetes. *Diabetes*, *52*(1),

851   102–110. https://doi.org/10.2337/diabetes.52.1.102

852   Campbell, I. W. (1976). The Somogyi phenomenon. A short review. *Acta Diabetologica*

853   *Latina*, *13*(1–2), 68–73. https://doi.org/10.1007/BF02591583

854   Cao, L., Liu, X., Lin, E.-J. D., Wang, C., Choi, E. Y., Riban, V., Lin, B., & During, M. J. (2010).

855   Environmental and Genetic Activation of a Brain-Adipocyte BDNF/Leptin Axis Causes

856   Cancer Remission and Inhibition. *Cell*, *142*(1), 52–64.

857   https://doi.org/10.1016/j.cell.2010.05.029

858   Carnethon, M. R., Jacobs, D. R., Sidney, S., & Liu, K. (2003). Influence of Autonomic Nervous

859   System Dysfunction on the Development of Type 2 Diabetes: The CARDIA study.

860   *Diabetes Care*, *26*(11), 3035–3041. https://doi.org/10.2337/diacare.26.11.3035

861   Chawla, S., Pund, A., B., V., Kulkarni, S., Diwekar-Joshi, M., & Watve, M. (2018). Inferring

862   causal pathways among three or more variables from steady-state correlations in a

863   homeostatic system. *PLOS ONE*, *13*(10), e0204755.

864   https://doi.org/10.1371/journal.pone.0204755

865   Chen, N.-G., Tassava, T. M., & Romsos, D. R. (1993). Threshold for Glucose-Stimulated

866   Insulin Secretion in Pancreatic Islets of Genetically Obese (ob/ob) Mice is Abnormally

867   Low. *The Journal of Nutrition*, *123*(9), 1567–1574.

868   https://doi.org/10.1093/jn/123.9.1567

869 Chodari, L., Mohammadi, M., Ghorbanzadeh, V., Dariushnejad, H., & Mohaddes, G. (2016).

870   Testosterone and Voluntary Exercise Promote Angiogenesis in Hearts of Rats with

871   Diabetes by Enhancing Expression of VEGF-A and SDF-1a. *Canadian Journal of Diabetes*,

872   *40*(5), 436–441. https://doi.org/10.1016/j.jcjd.2016.03.004

873 Clark, A., Jones, L., de Koning, E., Hansen, B. C., & Matthews, D. R. (2001). Decreased insulin

874   secretion in type 2 diabetes: a problem of cellular mass or function? *Diabetes*,

875   *50*(Supplement 1), S169–S171. https://doi.org/10.2337/diabetes.50.2007.S169

876 Coggan, A. R. (1991). Plasma Glucose Metabolism During Exercise in Humans. *Sports*

877   *Medicine*, *11*(2), 102–124. https://doi.org/10.2165/00007256-199111020-00003

878 Corkey, B. E., & Shirihai, O. (2012). Metabolic master regulators: sharing information among

879   multiple systems. *Trends in Endocrinology & Metabolism*, *23*(12), 594–601.

880   https://doi.org/10.1016/j.tem.2012.07.006

881 Cornford, E. M., Hyman, S., Cornford, M. E., & Clare-Salzler, M. (1995). Down-regulation of

882   blood-brain glucose transport in the hyperglycemic nonobese diabetic mouse.

883   *Neurochemical Research*, *20*(7), 869–873. https://doi.org/10.1007/BF00969700

884 Costes, S., & Butler, P. C. (2014). Insulin-degrading enzyme inhibition, a novel therapy for

885   type 2 diabetes? In *Cell Metabolism* (Vol. 20, Issue 2).

886   https://doi.org/10.1016/j.cmet.2014.07.016

887 D'Alessio, D. A., Kieffer, T. J., Taborsky, G. J., & Havel, P. J. (2001). Activation of the

888   Parasympathetic Nervous System Is Necessary for Normal Meal-Induced Insulin

889   Secretion in Rhesus Macaques1. *The Journal of Clinical Endocrinology & Metabolism*,

890   *86*(3), 1253–1259. https://doi.org/10.1210/jcem.86.3.7367

891 DeFronzo, R. A. (2010). Overview of Newer Agents: Where Treatment Is Going. *The*

892   *American Journal of Medicine*, *123*(3), S38–S48.

893   https://doi.org/10.1016/j.amjmed.2009.12.008

894 DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., Hu, F. B.,

895   Kahn, C. R., Raz, I., Shulman, G. I., Simonson, D. C., Testa, M. A., & Weiss, R. (2015).

896   Type 2 diabetes mellitus. *Nature Reviews Disease Primers*, *1*(1), 15019.

897   https://doi.org/10.1038/nrdp.2015.19

898   Diabetes Prevention Program Research Group. (2015). Long-term effects of lifestyle

899   intervention or metformin on diabetes development and microvascular complications

900   over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *The Lancet*

901   *Diabetes & Endocrinology*, *3*(11), 866–875. https://doi.org/10.1016/S2213-

902   8587(15)00291-0

903   Diwekar-Joshi, M., & Watve, M. (2020). Driver versus navigator causation in biology: The

904   case of insulin and fasting glucose. *PeerJ*, *8*. https://doi.org/10.7717/peerj.10396

905   Dungan, K. M., Braithwaite, S. S., & Preiser, J.-C. (2009). Stress hyperglycaemia. *The Lancet*,

906   *373*(9677), 1798–1807. https://doi.org/10.1016/S0140-6736(09)60553-5

907   Ferrannini, E., & DeFronzo, R. A. (2015). Impact of glucose-lowering drugs on cardiovascular

908   disease in type 2 diabetes. *European Heart Journal*, *36*(34).

909   https://doi.org/10.1093/eurheartj/ehv239

910   Gaohua, L., & Kimura, H. (2009). A mathematical model of brain glucose homeostasis.

911   *Theoretical Biology and Medical Modelling*, *6*(1), 26. https://doi.org/10.1186/1742-

912   4682-6-26

913   Ge, X., Chen, C., Hui, X., Wang, Y., Lam, K. S. L., & Xu, A. (2011). Fibroblast Growth Factor 21

914   Induces Glucose Transporter-1 Expression through Activation of the Serum Response

915   Factor/Ets-Like Protein-1 in Adipocytes. *Journal of Biological Chemistry*, *286*(40),

916   34533–34541. https://doi.org/10.1074/jbc.M111.248591

917   Gilon, P., & Henquin, J.-C. (2001). Mechanisms and Physiological Significance of the

918   Cholinergic Control of Pancreatic β-Cell Function. *Endocrine Reviews*, *22*(5), 565–604.

919   https://doi.org/10.1210/edrv.22.5.0440

920   Giustina, A., Girelli, A., Buffoli, M. G., Cimino, A., Legati, F., Valentini, U., & Giustina, G.

921   (1991). Low-dose octreotide is able to cause a maximal inhibition of the glycemic

922   responses to a mixed meal in obese type 2 diabetic patients treated with insulin.

923   *Diabetes Research and Clinical Practice*, *14*(1). https://doi.org/10.1016/0168-

924   8227(91)90052-F

925   Gjedde, A., & Crone, C. (1981). Blood-Brain Glucose Transfer: Repression in Chronic

926   Hyperglycemia. *Science*, *214*(4519), 456–457. https://doi.org/10.1126/science.7027439

927   Gray, S. M., & Barrett, E. J. (2018). Insulin transport into the brain. *American Journal of*

928   *Physiology-Cell Physiology*, *315*(2), C125–C136.

929   https://doi.org/10.1152/ajpcell.00240.2017

930   Gray, S. M., Meijer, R. I., & Barrett, E. J. (2014). Insulin regulates brain function, but how

931   does it get there? *Diabetes*, *63*(12), 3992–3997. https://doi.org/10.2337/db14-0340

932   Hasselbalch, S. G., Knudsen, G. M., Videbaek, C., Pinborg, L. H., Schmidt, J. F., Holm, S., &

933   Paulson, O. B. (1999). No effect of insulin on glucose blood-brain barrier transport and

934   cerebral metabolism in humans. *Diabetes*, *48*(10), 1915–1921.

935   https://doi.org/10.2337/diabetes.48.10.1915

936   Henquin, J.-C., Dufrane, D., & Nenquin, M. (2006). Nutrient Control of Insulin Secretion in

937   Isolated Normal Human Islets. *Diabetes*, *55*(12), 3470–3477.

938   https://doi.org/10.2337/db06-0868

939   Höppener, J. W. M., Oosterwijk, C., Nieuwenhuis, M. G., Posthuma, G., Thijssen, J. H. H.,

940   Vroom, T. M., Ahrén, B., & Lips, C. J. M. (1999). Extensive islet amyloid formation is

941   induced by development of Type II diabetes mellitus and contributes to its progression:

942   pathogenesis of diabetes in a mouse model. *Diabetologia*, *42*(4), 427–434.

943   https://doi.org/10.1007/s001250051175

944   Huang, Y., Lei, L., Liu, D., Jovin, I., Russell, R., Johnson, R. S., Di Lorenzo, A., & Giordano, F. J.

945   (2012). Normal glucose uptake in the brain and heart requires an endothelial cell-

946   specific HIF-1α–dependent function. *Proceedings of the National Academy of Sciences*,

947   *109*(43), 17478–17483. https://doi.org/10.1073/pnas.1209281109

948   Hwang, J. J., Jiang, L., Hamza, M., Sanchez Rangel, E., Dai, F., Belfort-DeAguiar, R., Parikh, L.,

949   Koo, B. B., Rothman, D. L., Mason, G., & Sherwin, R. S. (2017). Blunted rise in brain

950   glucose levels during hyperglycemia in adults with obesity and T2DM. *JCI Insight*, *2*(20).

951   https://doi.org/10.1172/jci.insight.95913

952   John Thomas Sorensen, --by, Colton Thesis Supervisor, C. K., & Deen, W. M. (n.d.). *A*

953   *PH'tSIOLOGIC MODEL OF GLUCOSE METABOLISM IN MAN AND ITS USE 1'0 DESIGN AND*

954   *ASSESS IMPROVED INSULIN THERAPIES FOR DIABETES SUBMITTED TO THE*

955   *DEPARTMENT OF*.

956   Kadowaki, T. (2000). Insights into insulin resistance and type 2 diabetes from knockout

957   mouse models. *Journal of Clinical Investigation*, *106*(4), 459–465.

958   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC380257/

959   Kern, W., Peters, A., Fruehwald-Schultes, B., Deininger, E., Born, J., & Fehm, H. L. (2001).

960   Improving Influence of Insulin on Cognitive Functions in Humans. *Neuroendocrinology*,

961   *74*(4), 270–280. https://doi.org/10.1159/000054694

962   Kiba, T. (2004). Relationships Between the Autonomic Nervous System and the Pancreas

963   Including Regulation of Regeneration and Apoptosis. *Pancreas*, *29*(2), e51–e58.

964   https://doi.org/10.1097/00006676-200408000-00019

965   King, P., Peacock, I., & Donnelly, R. (1999). The UK prospective diabetes study (UKPDS):

966   clinical and therapeutic implications for type 2 diabetes. *British Journal of Clinical

967   Pharmacology*, *48*(5), 643–648. https://doi.org/10.1046/j.1365-2125.1999.00092.x

968   Klein, R. (2010). Intensive treatment of hyperglycaemia: ACCORD. *The Lancet*, *376*(9739),

969   391–392. https://doi.org/10.1016/S0140-6736(10)61028-8

970   Krishnan, S., Chang, A. C., Stoltz, B. M., & Prasadarao, N. V. (2016). *Escherichia coli* K1

971   Modulates Peroxisome Proliferator–Activated Receptor γ and Glucose Transporter 1 at

972   the Blood-Brain Barrier in Neonatal Meningitis. *Journal of Infectious Diseases*, *214*(7),

973   1092–1104. https://doi.org/10.1093/infdis/jiw306

974   Laeger, T., Baumeier, C., Wilhelmi, I., Würfel, J., Kamitz, A., & Schürmann, A. (2017). FGF21

975   improves glucose homeostasis in an obese diabetes-prone mouse model independent

976   of body fat changes. *Diabetologia*, *60*(11), 2274–2284. https://doi.org/10.1007/s00125-

977   017-4389-x

978   Lakshmanan, J. (1986). Aggressive behavior in adult male mice elevates serum nerve growth

979   factor levels. *American Journal of Physiology-Endocrinology and Metabolism*, *250*(4),

980   E386–E392. https://doi.org/10.1152/ajpendo.1986.250.4.E386

981   Lam, T. K. T. (2005). Regulation of Blood Glucose by Hypothalamic Pyruvate Metabolism.

982   *Science*, *309*(5736), 943–947. https://doi.org/10.1126/science.1112085

983   Lamberts, S. W. J., & Hofland, L. J. (2019). Octreotide, 40 years later. In *European Journal of*

984   *Endocrinology* (Vol. 181, Issue 5). https://doi.org/10.1530/EJE-19-0074

985 Leahy, J. L., Bumbalo, L. M., & Chen, C. (1994). Diazoxide causes recovery of beta-cell

986   glucose responsiveness in 90% pancreatectomized diabetic rats. *Diabetes*, *43*(2).

987   https://doi.org/10.2337/diabetes.43.2.173

988 Lee, C. G., Heckman-Stoddard, B., Dabelea, D., Gadde, K. M., Ehrmann, D., Ford, L., Prorok,

989   P., Boyko, E. J., Pi-Sunyer, X., Wallia, A., Knowler, W. C., Crandall, J. P., & Temprosa, M.

990   (2021). Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes

991   Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care*,

992   *44*(12), 2775–2782. https://doi.org/10.2337/dc21-1046

993 Lerner, R. L., & Porte, D. (1972). Acute and steady-state insulin responses to glucose in

994   nonobese diabetic subjects. *Journal of Clinical Investigation*, *51*(7), 1624–1631.

995   https://doi.org/10.1172/JCI106963

996 Limenta, M., Ho, C. S. C., Poh, J. W. W., Goh, S.-Y., & Toh, D. S. L. (2019). Adverse Drug

997   Reaction Profile of SGLT2 Inhibitor-Associated Diabetic Ketosis/Ketoacidosis in

998   Singapore and their Precipitating Factors. *Clinical Drug Investigation*, *39*(7), 683–690.

999   https://doi.org/10.1007/s40261-019-00794-5

1000 Lipska, K. J., & Montori, V. M. (2013). Glucose Control in Older Adults With Diabetes

1001   Mellitus—More Harm Than Good? *JAMA Internal Medicine*, *173*(14), 1306.

1002   https://doi.org/10.1001/jamainternmed.2013.6189

1003 Liu, M., Cao, H., Hou, Y., Sun, G., Li, D., & Wang, W. (2018). Liver Plays a Major Role in FGF-

1004   21 Mediated Glucose Homeostasis. *Cellular Physiology and Biochemistry*, *45*(4), 1423–

1005   1433. https://doi.org/10.1159/000487568

1006 Lundqvist, M. H., Almby, K., Abrahamsson, N., & Eriksson, J. W. (2019). Is the Brain a Key

1007   Player in Glucose Regulation and Development of Type 2 Diabetes? *Frontiers in*

1008   *Physiology*, *10*. https://doi.org/10.3389/fphys.2019.00457

1009 Maianti, J. P., McFedries, A., Foda, Z. H., Kleiner, R. E., Du, X. Q., Leissring, M. A., Tang, W.-J.,

1010   Charron, M. J., Seeliger, M. A., Saghatelian, A., & Liu, D. R. (2014). Anti-diabetic activity

1011   of insulin-degrading enzyme inhibitors mediated by multiple hormones. *Nature*,

1012   *511*(7507), 94–98. https://doi.org/10.1038/nature13297

1013 Mari, A., Tura, A., Grespan, E., & Bizzotto, R. (2020a). Mathematical Modeling for the

1014 Physiological and Clinical Investigation of Glucose Homeostasis and Diabetes. In

1015 *Frontiers in Physiology* (Vol. 11, p. 1548).

1016 https://www.frontiersin.org/article/10.3389/fphys.2020.575789

1017 Mari, A., Tura, A., Grespan, E., & Bizzotto, R. (2020b). Mathematical Modeling for the

1018 Physiological and Clinical Investigation of Glucose Homeostasis and Diabetes. *Frontiers*

1019 *in Physiology*, *11*. https://doi.org/10.3389/fphys.2020.575789

1020 Marliss, E. B., & Vranic, M. (2002). Intense Exercise Has Unique Effects on Both Insulin

1021 Release and Its Roles in Glucoregulation: Implications for Diabetes. *Diabetes*,

1022 *51*(Supplement 1), S271–S283. https://doi.org/10.2337/diabetes.51.2007.S271

1023 Matsuda, M., Kawasaki, F., Mikami, Y., Takeuchi, Y., Saito, M., Eto, M., & Kaku, K. (2002).

1024 Rescue of beta-cell exhaustion by diazoxide after the development of diabetes mellitus

1025 in rats with streptozotocin-induced diabetes. *European Journal of Pharmacology*,

1026 *453*(1). https://doi.org/10.1016/S0014-2999(02)02389-0

1027 Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C.

1028 (1985). Homeostasis model assessment: insulin resistance and β-cell function from

1029 fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7).

1030 https://doi.org/10.1007/BF00280883

1031 Mehran, A. E., Templeman, N. M., Brigidi, G. S., Lim, G. E., Chu, K.-Y., Hu, X., Botezelli, J. D.,

1032 Asadi, A., Hoffman, B. G., Kieffer, T. J., Bamji, S. X., Clee, S. M., & Johnson, J. D. (2012a).

1033 Hyperinsulinemia Drives Diet-Induced Obesity Independently of Brain Insulin

1034 Production. *Cell Metabolism*, *16*(6), 723–737.

1035 https://doi.org/10.1016/j.cmet.2012.10.019

1036 Mehran, A. E., Templeman, N. M., Brigidi, G. S., Lim, G. E., Chu, K. Y., Hu, X., Botezelli, J. D.,

1037 Asadi, A., Hoffman, B. G., Kieffer, T. J., Bamji, S. X., Clee, S. M., & Johnson, J. D. (2012b).

1038 Hyperinsulinemia drives diet-induced obesity independently of brain insulin

1039 production. *Cell Metabolism*, *16*(6). https://doi.org/10.1016/j.cmet.2012.10.019

1040 Meneilly, G. S., & Tessier, D. M. (2016). Diabetes, Dementia and Hypoglycemia. *Canadian*

1041 *Journal of Diabetes*, *40*(1), 73–76. https://doi.org/10.1016/j.jcjd.2015.09.006

1042   Miller, R., Waid, T., & Joyce, M. (1976). Direct neural inhibition of insulin secretion in
1043   response to systemic hypoglycemia. *American Journal of Physiology-Legacy Content*,
1044   *230*(4), 1090–1094. https://doi.org/10.1152/ajplegacy.1976.230.4.1090

1045   Mistry, S., & Eschler, D. C. (2021). Euglycemic Diabetic Ketoacidosis Caused by SGLT2
1046   Inhibitors and a Ketogenic Diet: A Case Series and Review of Literature. *AACE Clinical*
1047   *Case Reports*, *7*(1), 17–19. https://doi.org/10.1016/j.aace.2020.11.009

1048   Muris, D. M. J., Houben, A. J. H. M., Schram, M. T., & Stehouwer, C. D. A. (2012).
1049   Microvascular Dysfunction Is Associated With a Higher Incidence of Type 2 Diabetes
1050   Mellitus. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *32*(12), 3082–3094.
1051   https://doi.org/10.1161/ATVBAHA.112.300291

1052   Nelles, E., Butzler, C., Jung, D., Temme, A., Gabriel, H. D., Dahl, U., Traub, O., Stumpel, F.,
1053   Jungermann, K., Zielasek, J., Toyka, K. V, Dermietzel, R., & Willecke, K. (1996). Defective
1054   propagation of signals generated by sympathetic nerve stimulation in the liver of
1055   connexin32-deficient mice. *Proceedings of the National Academy of Sciences*, *93*(18),
1056   9565–9570. https://doi.org/10.1073/pnas.93.18.9565

1057   NEXØ, E., HOLLENBERG, M. D., & BING, J. (1981). Aggressive behaviour in mice provokes a
1058   marked increase in both plasma epidermal growth factor and renin. *Acta Physiologica*
1059   *Scandinavica*, *111*(3), 367–371. https://doi.org/10.1111/j.1748-1716.1981.tb06749.x

1060   Nexø, E., Olsen, P. S., & Poulsen, K. (1984). Exocrine and endocrine secretion of renin and
1061   epidermal growth factor from the mouse submandibular glands. *Regulatory Peptides*,
1062   *8*(4), 327–334. https://doi.org/10.1016/0167-0115(84)90043-0

1063   Nguyen, T. T., Wang, J. J., & Wong, T. Y. (2007). Retinal Vascular Changes in Pre-Diabetes
1064   and Prehypertension. *Diabetes Care*, *30*(10), 2708–2715. https://doi.org/10.2337/dc07-
1065   0732

1066   Nonogaki, K. (2000). New insights into sympathetic regulation of glucose and fat
1067   metabolism. *Diabetologia*, *43*(5), 533–549. https://doi.org/10.1007/s001250051341

1068   ONO, T., STEFFENS, A., & SASAKI, K. (1983). Influence of peripheral and
1069   intracerebroventricular glucose and insulin infusions on peripheral and cerebrospinal
1070   fluid glucose and insulin levels. *Physiology & Behavior*, *30*(2), 301–306.

1071   https://doi.org/10.1016/0031-9384(83)90023-9

1072 Op den Kamp, Y. J. M., de Ligt, M., Dautzenberg, B., Kornips, E., Esterline, R., Hesselink, M. K.

1073   C., Hoeks, J., Schrauwen-Hinderling, V. B., Havekes, B., Oscarsson, J., Phielix, E., &

1074   Schrauwen, P. (2021). Effects of the SGLT2 Inhibitor Dapagliflozin on Energy

1075   Metabolism in Patients With Type 2 Diabetes: A Randomized, Double-Blind Crossover

1076   Trial. *Diabetes Care*, *44*(6), 1334–1343. https://doi.org/10.2337/dc20-2887

1077 Osundiji, M. A., Lam, D. D., Shaw, J., Yueh, C.-Y., Markkula, S. P., Hurst, P., Colliva, C., Roda,

1078   A., Heisler, L. K., & Evans, M. L. (2012). Brain Glucose Sensors Play a Significant Role in

1079   the Regulation of Pancreatic Glucose-Stimulated Insulin Secretion. *Diabetes*, *61*(2),

1080   321–328. https://doi.org/10.2337/db11-1050

1081 Pardridge, W. M., Triguero, D., & Farrell, C. R. (1990). Downregulation of Blood-Brain Barrier

1082   Glucose Transporter in Experimental Diabetes. *Diabetes*, *39*(9), 1040–1044.

1083   https://doi.org/10.2337/diab.39.9.1040

1084 Perrin, C., Knauf, C., & Burcelin, R. (2004). Intracerebroventricular Infusion of Glucose,

1085   Insulin, and the Adenosine Monophosphate-Activated Kinase Activator, 5-

1086   Aminoimidazole-4-Carboxamide-1-β- d -Ribofuranoside, Controls Muscle

1087   Glycogen Synthesis. *Endocrinology*, *145*(9), 4025–4033.

1088   https://doi.org/10.1210/en.2004-0270

1089 Pfützner, A., Klonoff, D., Heinemann, L., Ejskjaer, N., & Pickup, J. (2017). Euglycemic ketosis

1090   in patients with type 2 diabetes on SGLT2-inhibitor therapy—an emerging problem and

1091   solutions offered by diabetes technology. *Endocrine*, *56*(1), 212–216.

1092   https://doi.org/10.1007/s12020-017-1264-y

1093 Pories, W. J., & Dohm, G. L. (2020). Letter to the Editor Re: Sera of Obese Type 2 Diabetic

1094   Patients Undergoing Metabolic Surgery Instead of Conventional Treatment Exert

1095   Beneficial Effects on Beta Cell Survival and Function: Results of a Randomized Clinical

1096   Study. *Obesity Surgery*, *30*(9), 3603–3604. https://doi.org/10.1007/s11695-020-04665-

1097   3

1098 Porte, D., & Kahn, S. E. (1989). Hyperproinsulinemia and Amyloid in NIDDM: Clues to

1099   Etiology of Islet-Cell Dysfunction? *Diabetes*, *38*(11), 1333–1336.

1100   https://doi.org/10.2337/diab.38.11.1333

1101   Porte, D., & Kahn, S. E. (2001). Beta-cell dysfunction and failure in type 2 diabetes: potential

1102   mechanisms. *Diabetes*, *50*(Supplement 1), S160–S163.

1103   https://doi.org/10.2337/diabetes.50.2007.S160

1104   Rebelos, E., Rinne, J. O., Nuutila, P., & Ekblad, L. L. (2021). Brain Glucose Metabolism in

1105   Health, Obesity, and Cognitive Decline—Does Insulin Have Anything to Do with It? A

1106   Narrative Review. *Journal of Clinical Medicine*, *10*(7), 1532.

1107   https://doi.org/10.3390/jcm10071532

1108   Reyhanoglu, G., & Rehman, A. (2021). *Somogyi Phenomenon*.

1109   Rhee, S. Y. (2017). Hypoglycemia and Dementia. *Endocrinology and Metabolism*, *32*(2), 195.

1110   https://doi.org/10.3803/EnM.2017.32.2.195

1111   Rohner-Jeanrenaud, F., & Jeanrenaud, B. (1983). [The central nervous system-endocrine

1112   pancreas axis]. *Annales d'endocrinologie*, *44*(4), 217–227.

1113   Rosengren, A., Jing, X., Eliasson, L., & Renström, E. (2008). Why Treatment Fails in Type 2

1114   Diabetes. *PLoS Medicine*, *5*(10), e215. https://doi.org/10.1371/journal.pmed.0050215

1115   Schüler, R., Seebeck, N., Osterhoff, M. A., Witte, V., Flöel, A., Busjahn, A., Jais, A., Brüning, J.

1116   C., Frahnow, T., Kabisch, S., Pivovarova, O., Hornemann, S., Kruse, M., & Pfeiffer, A. F.

1117   H. (2018). VEGF and GLUT1 are highly heritable, inversely correlated and affected by

1118   dietary fat intake: Consequences for cognitive function in humans. *Molecular*

1119   *Metabolism*, *11*, 129–136. https://doi.org/10.1016/j.molmet.2018.02.004

1120   Schut, E. S., Westendorp, W. F., de Gans, J., Kruyt, N. D., Spanjaard, L., Reitsma, J. B., & van

1121   de Beek, D. (2009). Hyperglycemia in bacterial meningitis: a prospective cohort study.

1122   *BMC Infectious Diseases*, *9*(1), 57. https://doi.org/10.1186/1471-2334-9-57

1123   Schwartz, T. B., & Meinert, C. L. (2004). The UGDP Controversy: thirty-four years of

1124   contentious ambiguity laid to rest. *Perspectives in Biology and Medicine*, *47*(4), 564–

1125   574. https://doi.org/10.1353/pbm.2004.0071

1126   Shanik, M. H., Xu, Y., Skrha, J., Dankner, R., Zick, Y., & Roth, J. (2008). Insulin Resistance and

1127   Hyperinsulinemia: Is hyperinsulinemia the cart or the horse? *Diabetes Care*,

1128   *31*(Supplement 2), S262–S268. https://doi.org/10.2337/dc08-s264

1129   Shemesh, E., Rudich, A., Harman-Boehm, I., & Cukierman-Yaffe, T. (2012). Effect of

1130   Intranasal Insulin on Cognitive Function: A Systematic Review. *The Journal of Clinical*

1131   *Endocrinology & Metabolism*, *97*(2), 366–376. https://doi.org/10.1210/jc.2011-1802

1132   Shi, J., Dong, B., Mao, Y., Guan, W., Cao, J., Zhu, R., & Wang, S. (2016). Review: Traumatic

1133   brain injury and hyperglycemia, a potentially modifiable risk factor. *Oncotarget*, *7*(43),

1134   71052–71061. https://doi.org/10.18632/oncotarget.11958

1135   Shinde, S., Ranade, P., & Watve, M. (2021). Evaluating alternative hypotheses to explain the

1136   downward trend in the indices of the COVID-19 pandemic death rate. *PeerJ*, *9*, e11150.

1137   https://doi.org/10.7717/peerj.11150

1138   Stehouwer, C. D. A. (2018). Microvascular Dysfunction and Hyperglycemia: A Vicious Cycle

1139   With Widespread Consequences. *Diabetes*, *67*(9), 1729–1741.

1140   https://doi.org/10.2337/dbi17-0044

1141   Strachan, M W J. (2005). Insulin and cognitive function in humans: experimental data and

1142   therapeutic considerations. *Biochemical Society Transactions*, *33*(Pt 5), 1037–1040.

1143   https://doi.org/10.1042/BST20051037

1144   Strachan, Mark W J. (2003). Insulin and cognitive function. *The Lancet*, *362*(9392), 1253.

1145   https://doi.org/10.1016/S0140-6736(03)14615-6

1146   Templeman, N. M., Clee, S. M., & Johnson, J. D. (2015). Suppression of hyperinsulinaemia in

1147   growing female mice provides long-term protection against obesity. *Diabetologia*,

1148   *58*(10). https://doi.org/10.1007/s00125-015-3676-7

1149   Thackeray, J. T., Beanlands, R. S., & Dasilva, J. N. (2012). Altered sympathetic nervous

1150   system signaling in the diabetic heart: emerging targets for molecular imaging.

1151   *American Journal of Nuclear Medicine and Molecular Imaging*, *2*(3), 314–334.

1152   Thakar, J. D., Kunte, K., Chauhan, A. K., Watve, A. V., & Watve, M. G. (2003). Nectarless

1153   flowers: ecological correlates and evolutionary stability. *Oecologia*, *136*(4), 565–570.

1154   https://doi.org/10.1007/s00442-003-1304-6

1155   The NICE-SUGAR Study Investigators. (2009). Intensive versus Conventional Glucose Control

1156   in Critically Ill Patients. *New England Journal of Medicine*, *360*(13), 1283–1297.

1157   https://doi.org/10.1056/NEJMoa0810625

1158   Thorens, B. (2015). GLUT2, glucose sensing and glucose homeostasis. *Diabetologia*, *58*(2),

1159   221–232. https://doi.org/10.1007/s00125-014-3451-1

1160   Tirassa, P., Triaca, V., Amendola, T., Fiore, M., & Aloe, L. (2003). EGF and NGF injected into

1161   the brain of old mice enhance BDNF and ChAT in proliferating subventricular zone.

1162   *Journal of Neuroscience Research*, *72*(5), 557–564. https://doi.org/10.1002/jnr.10614

1163   Turner, R. C., Holman, R. R., Matthews, D., Hockaday, T. D. R., & Peto, J. (1979). Insulin

1164   deficiency and insulin resistance interaction in diabetes: Estimation of their relative

1165   contribution by feedback analysis from basal plasma insulin and glucose

1166   concentrations. *Metabolism*, *28*(11), 1086–1096. https://doi.org/10.1016/0026-

1167   0495(79)90146-X

1168   Turner, R., Matthews, D., Neil, a., & Mcelroy, H. (1998). Tight blood pressure control and risk

1169   of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *British*

1170   *Medical Journaledical*, *317*, 703–713. https://doi.org/10.1136/bmj.317.7160.703

1171   UK Prospective Diabetes Study (UKPDS) Group. (1998). *Intensive blood-glucose control with*

1172   *SU or insulin compared with conventional treatment (UKPDS 33) - Lancet 1998*.

1173   *352*(Ukpds 33), 837–853.

1174   van Veen, K. E. B., Brouwer, M. C., van der Ende, A., & van de Beek, D. (2016). Bacterial

1175   meningitis in diabetes patients: a population-based prospective study. *Scientific*

1176   *Reports*, *6*(1), 36996. https://doi.org/10.1038/srep36996

1177   Vibishan, B., & Watve, M. G. (2020). Context-dependent selection as the keystone in the

1178   somatic evolution of cancer. *Scientific Reports*, *10*(1), 4223.

1179   https://doi.org/10.1038/s41598-020-61046-7

1180   Watve, M. (2012). Doves, Diplomats, and Diabetes. In *Doves, Diplomats, and Diabetes*.

1181   https://doi.org/10.1007/978-1-4614-4409-1

1182   Watve, M. (2013). *Doves, Diplomats, and Diabetes*. Springer New York.

1183   https://doi.org/10.1007/978-1-4614-4409-1

1184 Watve, M., Bodas, A., & Diwekar, M. (2014). Altered autonomic inputs as a cause of
1185   pancreatic β-cell amyloid. *Medical Hypotheses*, *82*(1), 49–53.
1186   https://doi.org/10.1016/j.mehy.2013.11.002

1187 Watve, M., & Diwekar-Joshi, M. (2016). What to expect from an evolutionary hypothesis for
1188   a human disease: The case of type 2 diabetes. *HOMO*, *67*(5), 349–368.
1189   https://doi.org/10.1016/j.jchb.2016.07.001

1190 Watve, M., & Diwekar-Joshi, M. (2019). Does insulin signalling decide glucose levels in the
1191   fasting steady state? *BioRxiv*, 553016. https://doi.org/10.1101/553016

1192 Weyer, C., Hanson, R. L., Tataranni, P. A., Bogardus, C., & Pratley, R. E. (2000). A high fasting
1193   plasma insulin concentration predicts type 2 diabetes independent of insulin
1194   resistance: evidence for a pathogenic role of relative hyperinsulinemia. *Diabetes*,
1195   *49*(12), 2094–2101. https://doi.org/10.2337/diabetes.49.12.2094

1196 Wiebe, N., Ye, F., Crumley, E. T., Bello, A., Stenvinkel, P., & Tonelli, M. (2021). Temporal
1197   Associations Among Body Mass Index, Fasting Insulin, and Systemic Inflammation.
1198   *JAMA Network Open*, *4*(3), e211263.
1199   https://doi.org/10.1001/jamanetworkopen.2021.1263

1200 Yaffe, K. (2013). Association Between Hypoglycemia and Dementia in a Biracial Cohort of
1201   Older Adults With Diabetes Mellitus. *JAMA Internal Medicine*, *173*(14), 1300.
1202   https://doi.org/10.1001/jamainternmed.2013.6176

1203 Zaleska-Żmijewska, A., Piątkiewicz, P., Śmigielska, B., Sokołowska-Oracz, A., Wawrzyniak, Z.
1204   M., Romaniuk, D., Szaflik, J., & Szaflik, J. P. (2017). Retinal Photoreceptors and
1205   Microvascular Changes in Prediabetes Measured with Adaptive Optics (rtx1™): A Case-
1206   Control Study. *Journal of Diabetes Research*, *2017*, 1–9.
1207   https://doi.org/10.1155/2017/4174292

1208