

Can Persistent Children Hyperglycemia Be Induced by Causes Other Than Pancreas Failure?

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Abstract

In this work, children's persistent hyperglycemia has been revised using the available literature to support the proposed reasoning. Based on this study, we have shown that the human glycemic management system must be seen as coupled and integrated by four subsystems, namely, production system, consumption system, distribution system, control system, and also it should be seen as coupled to external noxious factors/stressors, if not we show that the glycemic homeostasis analysis might be defective and might induce, in many cases, a misdiagnosis of the causes of the persistent hyperglycemia under consideration. Also, in this work, some considerations were presented to show that anomalies in the cerebral glycemic control through the glucose sensor neurons might be a possible cause/origin of some of the glycemic abnormalities and dysfunctions (however, not only the known related hypoglycemia but also hyperglycemia) that occur in childhood. Finally, it is shown that persistent novel external noxious factors of modernity or noxious factors already known, but amplified by modernity, such as persistent stress, media induced fears, and phobias, environmental pollution, and electromagnetic pollution, can and should also be considered as possible precursors for the development of anomalies in the juvenile homeostatic glycemic system that might well be, if intense and persistent, the driver of the worldwide observed T1DM epidemic events.

Keywords

Juvenile Persistent Hyperglycemia, Body's External Noxious Elements, Glycemia's Sensor Neurons, Homeostasis, Euglycemia

1. Introduction

The regulation of blood glucose in the body basically depends on two fundamentals hormones, glucagon and insulin coupled many times to cortisol. These hormones dynamics are coupled to internal but also to external events such as stress,

in its several levels. The action of glucagon is to stimulate the production of glucose by the liver, and that of insulin, in opposition, is to block this production. Thus, they promote the adjustment of glucose homeostasis which is of paramount importance to avoid complications such as nondiabetic hyperglycemia or diabetes mellitus [1]-[8]. The maintenance of euglycemia is critical to preventing both hypoglycemia and hyperglycemia in this scenario, and the homeostasis process plays fundamental role (Figure 1, Figure is by: Shannan Muskopf from Biologycorner.com) [9] [10].

Since our main target here is to discuss children’s hyperglycemia at large, for the sake of a universal general definition of hyperglycemia and harmonization of terms, we refer here to the Encyclopedia Britannica (<https://www.britannica.com/science/hyperglycemia>):

“**hyperglycemia**, elevation of blood glucose concentrations above the normal range; it is the laboratory finding that establishes a diagnosis of diabetes mellitus. Hyperglycemia results from a decrease in the body’s ability to utilize or store glucose after carbohydrates are ingested and from an increase in the production of glucose by the liver during the intervals between meals. It is caused by a decrease in the production of insulin, a decrease in the action of insulin, or a combination of the two abnormalities. Mild hyperglycemia causes no symptoms, but more severe hyperglycemia causes an increase in urine volume and thirst, fatigue and weakness, and increased susceptibility to infection. Extremely high blood glucose concentrations result in loss of blood volume, low blood pressure, and impaired central nervous system function (hyperglycemic coma).”

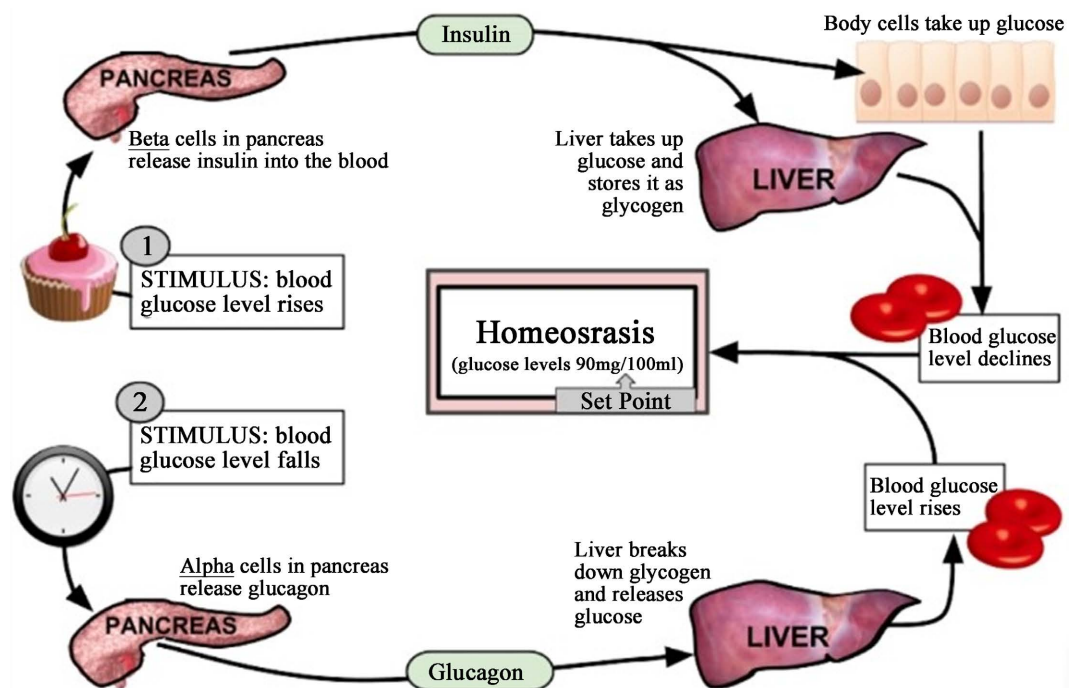


Figure 1. Shannan Muskopf (Worksheets).

Although external conditions are subject to variations, homeostatic mechanisms ensure that the effects of these changes are not noxious for organisms, if this mechanism works properly. Physiological glycemic levels are achieved through an integrated action between the different organs and systems that act in response to a set of blood glucose detection mechanisms, such as the glucose sensing neurons. These are highly developed systems; hence it is fundamental the role of hormones and electrical impulses in this control system; any anomalies can induce hyperglycemia or hypoglycemia. Anomalies in this system are highly harmful to humans [10].

An important remark is that this scheme (Figure 1) does not consider how the brain itself intervenes in this process for good or for bad. It is indeed a non-self-consistent way to see the real self-consistent homeostatic system. The correct approach is to consider this systems coupled to the Hypothalamic-Pituitary-Adrenal (HPA) axis, the Gut-Brain (GB) A axis, the Gut-Liver-Brain (GLB) axis, Microbiota-Gut-Liver-Brain (MGLB) axis and to the brain as a unit itself, in general. The brain, the gut, and the HPA axis connect the external world with the human body, and so they must be influenced by external noxious elements that might affect the body glucose homeostatic dynamics somehow. More intense the coupled external events, more fluctuations in the glucose blood level.

The glucose homeostasis requires the organism to respond quickly to changes in plasma glucose concentration. If the blood glucose concentration rises above normal, insulin is released, which stimulates the body's cells to remove glucose from the blood. If the blood glucose concentration drops below the normal level, glucagon is released, which stimulates the body's cells to release glucose into the blood. The first response to a drop in glucose is detection of impending hypoglycemia by the hypoglycemia sensing sensors, including glucose sensing neurons in the hypothalamus and other regions. This detection is then linked to a series of neural and hormonal responses that serve to prevent blood glucose from falling and restore euglycemia. Hence, the fundamental role of the brain (sensor neurons) in the glucose control/homeostasis system and the maintenance of euglycemia is of paramount importance and have to be accessed and understood [8] [9] [10] [11]. Therefore, it is in order to investigate further how the brain anomalies, due internal or external anomalies driver factors, can contribute, by loosing capacity of detection or by generating spurious signals/synapses, to induce imbalances in blood glucose levels, as the persistent hyperglycemia. Here, we discuss the current state of knowledge about the central glucose detection and how the detection of a drop in glucose level may (or may not) lead to stimulation of counter regulatory hormones and related behavioral responses. Impaired awareness of hyperglycemia, which is an impaired ability to perceive the onset of hyperglycemia, is associated with an increased risk of severe hyperglycemia in non-diabetic people. Accessing the pathogenesis might help to minimize the risk of severe hyperglycemia. Knowing that glucose is just a type of sugar

which is a generic name assigned to any type of naturally sweet, in different degrees, carbohydrates, and that they are divided into two categories, that is, monosaccharides-glucose, fructose and galactose and disaccharides, which is sucrose, lactose and maltose. Therefore, in order to control the intake of it all to guarantee the euglycemia, it is a highly complicated task to our body.

All these complexities are closely associated with the feedback mechanism. The feedback mechanism is known from the literature as a set of responses produced by our body to face changes in the daily life body requirements. In order to function perfectly, the human body relies on a series of essential mechanisms, such as positive and negative feedback mechanisms. Negative feedback is one of the most important mechanisms for maintaining our body's homeostasis, that is, for internal balance. This mechanism guarantees an opposite change in relation to the initial input, that is, it produces responses that reduce the initial stimulus. Thus, if a variable has a value below or above normal, such as the body temperature, it will try to increase or decrease this value, accordingly. Hormonal pathways, for example, have negative feedback as their main regulation, more details can be found in the following references.

The positive feedback, unlike the negative one, guarantees the increase of the stimulus that causes imbalance, reinforcing it. A good example is the regulation of the amount of glucose in the blood. An exaggerated increase or decrease in sugar levels can trigger problems in the body, so it is essential to keep levels within the ideal range. When we eat, the blood glucose level increases, causing more insulin to be produced. This hormone ensures that the cells absorb glucose and store its excess in the form of glycogen, thus reducing blood sugar levels. When glucose levels drop, insulin stops being released. When sugar levels are below normal, glucagon secretion occurs. This hormone, unlike insulin, releases glucose that is stored in liver in the form of glycogen, causing levels of this substance to increase in the blood. Thus, with increasing glucose levels, glucagon secretion stops. When for some reason there is danger of hypoglycemia detected by the brain's glucose-sensing neurons, an electrical impulse is also emitted to return euglycemia. In a situation of danger, the brain through the sensor neurons stimulates the HPA axis so that more glucose/energy is produced to face the danger, once the danger is removed the brain through the glucose sensor neurons commands the HPA axis to interrupt the stimulus to the liver to produce glucose, and to pancreas, and euglycemia is reached again. It is very clear that if there are anomalies (internal/external) in this control system that does not allow glycaemic homeostasis (negative feedback) to return the system to euglycemia, hyperglycemia or hypoglycemia will set in, hypoglycemia is more severe and urgent and immediate measures are needed to eliminate it as the person is immediately life threatening situation, but in the case of hyperglycemia, as the body tolerates this condition for some time, the person may even develop persistent hyperglycemia and subsequent diabetes mellitus over time such T2DM and T1DM [12] [13]. The most severe persistent hyperglycemia driver, with reasonable clear causes, in most of the cases, is maybe the T1DM.

The Johns Hopkins Diabetes Guide states:

(https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_Diabetes_Guide/All_Topics/A):

“Type 1 diabetes: complete or almost complete insulin deficiency, usually caused by autoimmunity. Clinical features: younger onset (usually but not always before 30 years old), normal body weight, usually no family history of diabetes, insulin treatment required immediately or within about a year, positive GAD, IA2 and/or islet cell antibodies, susceptibility to ketoacidosis and unstable blood glucose levels.”

The question to be asked is: Is there any other reasons for children’s hyperglycemia, insulin dependent, apart from T1DM? Can the persistent hyperglycemia induced by any internal or external causes due to a feedback error induce pancreas exhausting to insulin rather than beta cells’ death? This being true, in this case, once ceasing pancreas’ exhaustion causes, it might well be that the hyperglycemia will be extinguished/controlled.

It is also very clear from the literature that our brain plays a leading role in controlling glycemic changes due to external effects such as stress, danger, pollution, and electromagnetic fields present in today’s technologies (cell phone, wifi, wireless equipment’s, etc.), all the original details can be seen in references that follows [14] [15] [16]. It can be speculated that all kinds of stressors to the brain, in a “always present way”, can indeed cause persistent hyperglycemia, a typical example of a noxious external element is the persistent mental stress induced by stressful work which might cause the well-known “burnout” or chronic fatigue syndrome (CFS) (“exhaustion syndrome”) [17] [18] [19] [20].

As mentioned in references below and references therein, the brain certainly “knows” how to respond to stressful life situations, but up to a certain limit, if it has passed the point of balance, the brain can generate spurious synaptic signals, either for glycemic control or for another type of control or action, since persistent stresses can even change the morphology of the brain causing harmful effects on the person’s synapses and even physical health including diabetes, if those stressful conditions are persistent/chronic, as we will see later in this paper a good example of that is the type 3 diabetes [21] [22] [23]. Taking in consideration that there is no systematic study on the complete integrated body’s glucose management system (to the best of our knowledge), we want to contribute to this issue further with some observations on what could be considered in order to improve the general research targets on this issue and how to improve the general diagnosis methods of juvenile nondiabetic persistent hyperglycemia and T1DM.

What we could call here a methodology of research can be described as follows: The human glycemic system is mainly related to brain, HPA axis, pancreas, kidney, gastrointestinal tract, other related axes (to be described below), and skeletal muscles. Therefore, in order to access this highly nonlinear coupled system, we investigated in the literature each specific affected area of the hu-

man's body to grasp how each of those areas "see" the problem of the human glycemi, and how they model the problem in order to restore the euglycemia in their different situations.. In order to do that, we investigate in literature the way endocrinologists see the problem, then the neurologists, the neuroendocrinologists, the cardiologists, the sport areas, and finally the nephrologists and some other transversal areas/topics related to this theme. For instance, areas related to body infection and inflammation, and also to the glycemic dynamic in hospitalization conditions. This reasoning is supported by in the references list in this paper and the references therein. Based on those not systematized specialists' visions and in the general investigated literature, we arrived to the proposals and conclusions described in this paper. In short, the target here is to create an alternative paradigm, or at least a broader discussion, on both research and clinic in order to investigate the children/youth hyperglycemia in an integrated way envisaging new harder integrated tools of research and diagnosis.

This paper is organized as follows, in section 2, we presented a discussion to revise how the persistent hyperglycemia build up in children and also introduce the concept of body glucose integrated management system, in section 3, we discuss the current paradigm, and in section 4, we presented the conclusions, and the references follows. Paradigm here is considered as described by Thomas Kuhn in his book, "The Structure of Scientific Revolutions (first published in 1962), he defines a paradigm as: 'universally recognized scientific achievements that, for a time, provide model problems and solutions for a community of practitioners, *i.e.*, what is to be observed and scrutinized.'"

2. Integrated Human Body Glucose Management System

In order to keep the body general homeostasis, it is necessary to have a health feedback control system, as in the specific case of the glucose homeostasis. The body glucose management system is complex, multivariable, and highly nonlinear, and so to keep the glucose homeostasis it is not a trivial task to our body and it is becoming a task with more complexity due to the intense modern life demands and noxious elements from different sources.

The homeostasis can be influenced by either internal body conditions (intrinsic factors) or external conditions (extrinsic factors), and it is maintained by many different mechanisms.

- A sensor or receptor that detects changes in the internal or external environment. An example is peripheral chemoreceptors, which detects changes in blood ph.
- The integrating center or control center receives information from the sensors and initiates the response to maintain homeostasis. The most important example is the hypothalamus, a region of the brain that controls everything from body temperature to heart rate, blood pressure, satiety (fullness), and circadian rhythms (including, sleep and wake cycles).
- An effector is any organ or tissue that receives information from the integrat-

ing center and acts to bring about the changes needed to maintain homeostasis. One example is the kidney, which retains water if blood pressure is too low.

The sensors, integrating center, and effectors are the basic components of every homeostatic response. Positive and negative feedback are more complicated mechanisms that enable these three basic components to maintain homeostasis for more complex physiological processes. The global human glucose management dynamics, described in the introduction, that is: uptake, distribution, use, control to be well understood must necessarily be divided into phases or systems, which might be as below:

- Production System.
- Distribution System.
- Consumption System.
- Control System.

The pictorial views of these systems are shown below in **Figure 2** and **Figure 3**.

Note that we consider the external glucose input integrated at the production subsystem. For the body to function continuously, those systems must function automatically and in a synergetic way. Synergetic in the sense that the sum of the efficiencies of the parts is less than the efficiency of the integrated system, that is, looking at the system in a fragmented way impairs the look of the system synergetic dynamics, "2 + 2" = "5". It also impairs the view on the system self-consistency, which refer here as the property of an event A generating an event B and an event B generating an event A, A and B form a coupled system. In the human glycemic issues, the two above fundamental properties need to be considered carefully in order to evaluate the dynamics of hyperglycemia and hypoglycemia by means of research or diagnosis. This integrated view at the functioning of the human glycemic system (homeostasis-feedback and the consequent euglycemia

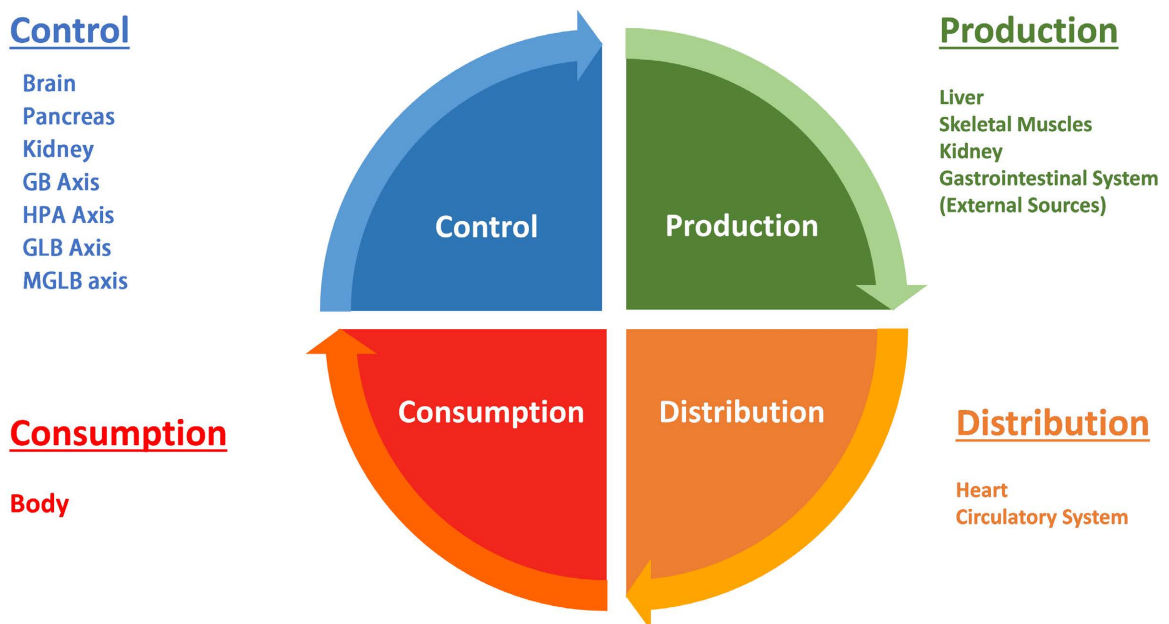


Figure 2. The four glucose synergetic subsystems.



Figure 3. Integrated glucose management system.

or disease) is what constitutes the basis of this proposal. What about persistent childhood hyperglycemia just caused by genetic problems, pancreas failure, or are there other plausible and checkable possibilities for this anomaly? For obvious reasons, one cannot simply ignore the hypotheses of the current paradigm, such as failures in the pancreas and problems in the immune system, but one cannot neglect the hypotheses raised in this proposal based on a significant number of related works, some referenced in the previous paragraphs. The description of the function of each system will be presented below.

A management system is the way in which an organization manages the interrelated parts of its business in order to achieve its objectives (ISO definition). By management system here, we mean that the above four coupled systems must be seen as integrated processes designed precisely to assure an appropriate production, distribution, utilization, and control of glucose resources which are managed (as an integrated management system by the body) to the day-to-day body operation such as in physical activities and on synopsis demands, in short it is the way our body manages the interrelated parts of its glycemic functions.

The “business” here is to keep the body’s euglycemia.

2.1. The Production System

The body glucose production is manufactured internally and externally. The external glucose intakes is obtained from food directly through the sugar in fruits and processed foods or indirectly through its by-products. External glucose/sugar intake is mediated by the gastrointestinal tract/hormones, mainly stomach and small intestine, and which plays a key role in its absorption and metabolism metabolization due to its (intestine) straight relation to the brain might also impact the brain glucose control functioning due to its wired feedback system. The gastrointestinal tract is a paramount importance interface for the exchange between ingested food (and so glucose) and the body, basically the system stomach-small intestines, which is where most of food digestion occurs.

The production of internal glucose is performed primarily by the liver, and in a more complementary way by the skeletal muscles. The kidney also produces some glucose, but in small volumes, in special situations. That is, the energy/glucose supply to the body goes through an extremely complex and integrated route where any failure in one of the systems can cause hypoglycemia or hyperglycemia. Hypoglycemia is immediately signaled by the brain through sensor neurons, because there is a danger of death. Hyperglycemia is signaled more indirectly by factors such as heavy urination and other signs, but there is no total body shutdown in hyperglycemia regime as in the case of hypoglycemia one, although prolonged hyperglycemia without medical attention is highly harmful to body as well [24].

External intake (food) brings all types of sugar to our body, such as sucrose which is made of a molecule each of glucose and fructose, lactose is made of one molecule of glucose and another of galactose, and maltose is made of two glucose molecules. Sugar are, mainly, called monosaccharides such as glucose and galactose and disaccharides such as lactose, sucrose, and maltose (as carbohydrate there also polysaccharides such as starch and cellulose) (<https://byjus.com/biology/polysaccharides/>).

However, the key source of energy is glucose; it is, as well-known, body’s selected carb-based energy source; it stimulates the release of insulin in the pancreas, and as known insulin is needed for glucose to enter into cells. Glucose and fructose are absorbed directly into our bloodstream from the small intestine, since they are monosaccharides or simple sugars (also galactose) having only one molecule (<https://www.healthline.com/nutrition/sucrose-glucose-fructose#absorption-and-use>).

Since disaccharides are made up of two molecules, two linked monosaccharides, they must be broken back down to a simple molecule structure during digestion to be able to be absorbed. For instance, sucrose is made of a molecule each of glucose and fructose, lactose is made of one molecule of glucose and another of galactose, and maltose is made of two glucose molecules. So, as al-

ready well known, when, for instance, the lactose reaches the digestive system, the lactase enzyme breaks it down into glucose and galactose. The liver then changes the galactose into glucose, which enters the bloodstream and raises the person's blood glucose level. In this scenario, either directly or indirectly via a disaccharide, the glucose increases blood sugar faster than the other sugars, it induces insulin to be produced to keep the euglycemia

(<https://www.news18.com/news/lifestyle/sugar-glucose-fructose-sucrose-lactose-benefits-harm-myupchar-3190874.html>)

This already complicated and nonlinear sugar intake and absorption dynamics must be coupled to, and it is indeed coupled, a highly precise control system that includes the brain-gut axis.

It is also in order to be aware of the importance of the gut-liver-brain axis, the microbiota-gut-brain axis, and the microbiota-gut-liver-brain axis as well. These systems deserve a further study related to the full control of the glucose management system, mainly the latter that has attracted increased attention in recent years, in the digestive diseases scenario (World J Gastroenterol 2020 October 28; 26(40): 6141-6162).

2.2. The Distribution System

The distribution of glucose throughout the body to be used as fuel to create energy is made by the blood and mediated/controlled/impacted mainly by organs such as liver, intestine, pancreas, kidney, heart, and Brain/HPA axis [25] [26] [27]. The glucose circulating level is impacted by external and internal factors such as infections, stress, fears and phobias, physical and intellectual activities, etc. Internally, the largest customers for glucose consumption are the brain (in its multiple cognitive and emotional functions) and the heart, and of course, the skeletal muscles, most of them with binary functions of customer and “service” provider [28] [29]. We are considering in this paper only the macroprocesses for the children glucose dynamic, therefore we are not accessing here details on the transport of glucose into the cells itself, which is a local microprocess for each cell, and indeed this is a more specific and special issue and highly complex subject to be addressed coupled to the macroprocesses in future work. In this scenario, the triad glucose - insulin-ATP has to work synergetically and perfectly well with cells in order to permit the creation, distribution, and storage of energy, which is of paramount importance for normal life dynamics [6] [25]. Glucose is the fuel for the cells energy generation, but it only turns to ATP/energy inside the cells. ATP can be used to store energy for future reactions or be taken out to pay for reactions when energy is required by the cells [25]. In this scenario, glucose and insulin are distributed throughout the body to power each and every cell of our body giving us the sensation of energy and well-being.

2.3. Consumption System

As can be seen in the above references, the consumption of glucose actually oc-

curs distributed throughout the body, in each cell there is energy production with the primary use of glucose, mediated by the ATP. As seen previously, the main customer of glucose is the brain that consumes 20% of the volume produced to maintain its fundamental neural network functions for cognition, general control and emotions, all consume energy that needs to be supplied somehow. The other organs and muscles also need glucose in bulk, like the heart. This consumption needs to be supplied and controlled online, continuously, failures in this supply lead to serious problems in the functioning of our body such as hypoglycemia [30] [31].

The supply, distribution, and use of energy via glucose fueling must be perfectly integrated with the dynamics of absorption and control of this energy via basically insulin and glucagon that stimulate or inhibit this production. In situations of stress or danger, the HPA axis stimulates the pancreas via the hormone cortisol and the pancreas releases the hormone glucagon which in turn stimulates the liver and controls insulin release so that the body has more energy available for use [32].

It is also important to mention the role of the adrenal norepinephrine that like the epinephrine (Adrenaline) also increases the heartbeat and the blood sugar level. Glucagon and catecholamines (norepinephrine and dopamine) stimulate also net hepatic glucose flux via the increasing of the hepatic glucose production mediated by glycogenolysis and gluconeogenesis. As might well be learned from the references that follow, the hyperglycemia can continue due to the mediation of epinephrine on gluconeogenesis and glucose disposal persist, once adrenaline triggers the body's fight-or-flight response.

Norepinephrine is, as well known, related also to stress, both epinephrine and norepinephrine increase blood sugar level and both can connect stress to body sugar level, we will come back to this Important theme of glycemia and stress later in this work.

This dynamic of energy control and use on demand as in danger or for the body's endogenous needs as in the case of infections is strongly nonlinear and involves diverse hormones and a range of complex electrical impulses. The HPA axis, HPG axis, HPT axis and the hypothalamic-neurohypophyseal system are the four major neuroendocrine systems through which the hypothalamus and pituitary drive neuroendocrine functions, they are integrated somehow, via brain, and introduce a great deal of complexity in human glucose homeostasis and energy release and use [27] [28]. Building up and "burning" glucose is a trick operation and pancreas can get really "tired" and sick of producing insulin and glucagon, if the proper feedback system fails to adjust to changes, "exhausted" pancreas, not sick, might be a reality in many situations diagnosed as sick pancreas. Imbalance between the production of insulin and glucagon and a continuously demand can induce hypoglycemia or hyperglycemia, and this can be related to beta cells physiological dynamics and dysfunctional activities, and possibly exhaustion and compromised cell identity. Immune system play role in a dysfunctional pancreas activity, but it is not the only one, as we can learn from

the references quoted and therein [33] [34] [35].

2.4. Control System

The circulating blood glucose needs to be controlled so that there is neither hypoglycemia nor hyperglycemia, both of which are highly harmful to the body [36] [37] [38]. The blood glucose control system first involves the brain as a central control, then the HPA axis, liver, pancreas, Gut-brain axis, and the skeletal muscles that also act in case of lack of glucose from the normal controlled circuit liver-pancreas. Basically, blood glucose control is done by electrical impulses and key hormones such as cortisol, glucagon, and insulin, so to speak, but in fact the highly complex biochemistry reactions are involved. In order to control the glucose level circulation, it is necessary a system of specialized sensors to sense blood glucose variations, the brain through the hypothalamus has dedicated to detecting hypoglycemia. Hypoglycemia is fatal and the brain works so that the body is somehow protected from this condition. In the hypothalamus and other regions of the brain there are neurons dedicated to this task. For hyperglycemia, as far as can be seen, there are no articles in the literature that mention regions, with no caveat, of the brain with neurons dedicated to detecting hyperglycemia and clearly controlling it, but they certainly exist in view of the indirect signaling of this condition, such as: Polyuria (excess urine) and polydipsia (thirst), pain, numbness, tingling of the legs, blurred and blurry vision and itching in the genital regions may also appear, which clearly show that the brain also acts directly, although differently, in hyperglycemia as in hypoglycemia [39]-[57].

In conclusion, for this part of the proposal, considering what was described above, it can be said that any attempt to diagnose or cure glycemic anomalies, whether hypo or hyper, persistent or not, must consider necessarily an integrated approach of those systems and known clearly what is impacting what and why. A failure in one of these systems impacts the others in some way. For example, an error in the brain's control of hypoglycemia can induce hyperglycemia without the pancreas being sick. Sick or not, the body will always continue to demand energy/glucose for its energy needs to stay alive, and the dysfunction needs to be corrected. The brain knows this very well and reduces the entire system to a minimum expenditure to maintain vital functions even under low energy/glucose regime (hypoglycemia), commonly manifested as fainting. It is important to mention that circulating energy/glucose does not imply energy for the body, glucose only turns into energy once inside the cell via ATP, hyperglycemia does not imply hyper energy, on the contrary, hyperglycemia due to an insulin problem often causes fatigue and lack of energy. Glucose is the source for energy generation, but it only turns ATP/energy inside the cells. As already said, ATP can be used to store energy for future reactions or be taken out to pay for reactions when energy is required by the cell. Animals store the energy obtained from breaking down food as ATP [58].

The importance of the role played by the brain in the glucose control system can be exemplified by the Type 3 diabetes disease, there is also, of course, the

biochemical complexity in the transformation of glucose into energy and the subsequent storage and this shows how it is indeed possible to appear dysfunctions in blood glucose level, strange sometimes, associated with the consumption, control, and use of energy by the body. For instance, a good example of dysfunction in glucose brain control, as said, is the not well known Type 3 diabetes that occurs when some neurons in the brain become not capable to respond properly to insulin, which is of paramount importance for daily “trivial” tasks, such as memory and learning. There is a believe that insulin deficiency can play central role to the cognitive decline of Alzheimer’s disease and this reasoning is well described by By Lynda De Widt, in Researchers link Alzheimer’s gene to Type 3 diabetes, October 25, 2017, <https://newsnetwork.mayoclinic.org/>, further details on Type 3 diabetes can be found on references that follows [59] [60]. Harmful internal and external agents that can generate anomalies in these four systems are the following: Spurious electrical signals from the brain, anomalies in the organs involved in each system, persistent external noxious agents such as stress, fears and phobias, electromagnetic pollution, and contamination by persistent pollutants and/or heavy metals, the persistent organic pollutants and toxic metals in foods is a standard reference for those in the food industry safety and this is well described in the book edited by Martin Rose and Alwyn Fernandes: Persistent Organic Pollutants and Toxic Metals in Foods, Woodhead Publishing Series in Food Science, Technology and Nutrition, 2013, Pages 430-475. It is in this scenario that the control system plays fundamental role for the body to be glucose-sick or to be glucose-health.

3. Criticism of the Current Paradigm

In general, the diagnosis of the causes of persistent childhood hyperglycemia, with no obesity causes, is mainly anchored (but not only of course) on indicators of T1DM [61] [62] [63] [64] [65]. As described in the above literature and references therein, it can be said that the T1DM is as a condition in which the pancreas does not produce insulin and is usually diagnosed at a young age and the baseline diagnosis is closely associated with measurements of glycated hemoglobin (glycosylated hemoglobin test), which is a form of hemoglobin that is chemically linked to a sugar. As mentioned there, most of monosaccharides, including glucose, galactose, and fructose, spontaneously bind to hemoglobin when present in the bloodstream of humans. It is also mentioned there that the investigation of glycated hemoglobin in the blood, also known as HbA1C or A1C, is the main test indicated when investigating diabetes. The standard then in the current paradigm is to decree that at a normal blood glucose level the A1C is below 5.7%, a level of 5.7% to 6.4% indicates prediabetes, and a level of 6.5% or more indicates diabetes, so to speak, with variations of metrics. Within the prediabetes range of 5.7% to 6.4%, the higher the A1C, the greater the risk of developing T2DM. There is also the HOMA index (Homeostasis Model Assessment) which is also an indicator used to diagnose the insulin resistance issues, that is: (HOMA-IR), and pancreas activity (HOMA-BETA), and thus useful to assist the diagnosis of

T2DM (IR) and T1DM (BETA).

As can be learned from the literature that follow and references therein, another important indicator of persistent hyperglycemia is the C-peptide which is measured in its amount in blood or urine sample. As broadly known the C-peptide, which is a short chain of amino acids, produced when proinsulin splits to form two molecules, one is the C-peptide and the other is the insulin. The C-peptide is produced at the same rate as insulin, which makes it a useful marker of insulin production [66] [67] [68] [69]. It is important to mention that in many “real world” situations, in diagnosis, the typical indicators of T1DM are not present, in full, even if when the body is working in regime of persistent hyperglycemia, and so the term idiopathic is used to mitigate the ignorance of the reason for the observed persistent hyperglycemia, which for sure is certainly hidden in dysfunctions of some of the four systems described in this work. In this way, it is in order to investigate carefully further those four coupled systems in its dynamics. It is worth to mention here, as described in the paper that follows, that in medical terms “The term idiopathic is often used to describe a disease with no identifiable cause”. It may be a diagnosis of exclusion; however, what specific minimum investigations need to be performed to define idiopathic is not always clear. This commentary describes the problems inherent in reaching a definition for the term idiopathic. “There is limited literature describing methodology to define a condition with no clear diagnostic criteria”. “It is important to correctly develop these standardized definitions for use as outcome measures in research and as clinical indicators in healthcare”. To these quotes refers to Tirlapur SA, Priest L, Daniels JP, Khan KS; MEDAL Study Management Group. How do we define the term idiopathic? *Curr Opin Obstet Gynecol*. 2013 Dec; 25(6): 468-473.

The most common types of diabetes that are used to explain children hyperglycemia in the current paradigm described in the literature are the T1DM and T2DM, and some others not so habitual, such as Type 1b or idiopathic diabetes seen by the specialists as an unusual form of phenotypic type 1 diabetes with almost complete insulin deficiency, a strong hereditary component, and no evidence of autoimmunity reported mainly in Africa and Asia, for more details on that refers to

https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Diabetes_Guide/547038/all/Diagnosis_and_Classification_of_Diabetes.

Our main goal here is just the access the nondiabetic hyperglycemia and the T1DM. It is in order to say that those classification and diagnosis are not in general so accurate, many of the diagnoses are not precise and causing even misleading conclusions and, in fact, there are other types of diabetes that are not well known such as type 3, still under study in the related literature presented [59]. And even type 4 diabetes which isn't also an autoimmune condition like type 1 diabetes (formerly called juvenile-onset or insulin-dependent diabetes mellitus) and not linked to weight like type 2 diabetes (formerly called adult-onset or non-insulin dependent diabetes mellitus) instead, this potential type of diabetes

may be linked to the aging process. You might also hear terms, such as Monogenic Diabetes, Latent Autoimmune Diabetes in Adults (LADA). There is also the so named Brittle diabetes which is also known as unstable diabetes or labile diabetes as can be seen in the general related literature.

When the real cause of a diagnosed persistent hyperglycemia is not known they call it, in general, idiopathic diabetes, and for sure this is so because the systems 1 - 4 described above were not evaluated correctly, for the patient under analysis. The Type 2 diabetes, in many cases, appears later in life, when, according to related literature, the pancreas cannot produce enough insulin to keep up with the body. The third type, Type 3c diabetes develops, according to the literature, because of damage to the pancreas, which can happen for different reasons. Although it is different from other types, it is very possible, as the related literature remarks, to get a misdiagnosis of type 2 because type 3c is not well known. That is, the diagnosis of glucose and related dynamic problems is not trivial and need to be studied in a systematic way in all its systems described above [70] [71] [72]. It is worth now discussing a little more about the current paradigm for the diagnosis and treatment of abnormalities in human blood glucose, the focus here is on persistent childhood hyperglycemia.

Persistent childhood hyperglycemia has induced most of the diagnoses of diabetes mellitus, in general, either T1DM related to pancreas fail or T2DM more related to obesity and other causes. In the vast literature and related medical diagnoses investigated, persistent hyperglycemia (infantile or otherwise) is considered to be associated with diabetes mellitus - DM, and this conclusion is never based on a thorough and meticulous investigation of the integrated human glycaemic system, items (1) - (4) above. The Hyperglycemia is generally attributed to failure of the pancreas and the consequent lack of sufficient insulin to contain excess glucose in the body. The standard treatment in most diagnoses and countries is the use of artificial insulin, that is, it is a worldwide medical standard. The WHO considers the number of T1DM cases in the world to be epidemic, as it is high annually and maintains a consistent pattern of growth over the years [66].

Basically, T1DM has no cure in the current paradigm of medical action in childhood persistent hyperglycemia, what is made to mitigate its effects is using dietary therapies, proper exercises such as breathing and others, and insulin intake [64]. What the description of the system (1) - (4) shows is that it is essential to change the paradigm of medical intervention/diagnosis in dealing with childhood hyperglycemia. It became very clear the fundamental role of the brain that, more than a client of blood glucose it plays a key role in its control, this binary function of the organs as a client and as part of the system has not been consistently investigated by doctors and researchers in the area, with rare some few exceptions of course. With the above reasoning, it is very clear why a cure has not yet been found for many cases of T1DM (idiopathic or not). In conclusion, for the real search for a cure for T1DM and not just the mitigation of the noxious effects, and for a more accurate diagnosis, it is necessary:

(1) To investigate the anomalies of persistent childhood hyperglycemia in an

integrated way by the proposed four systems (1) - (4) already described;

(2) To consider the human glucose-related organs such as Brain, HPA and the other related axes, Pancreas, Liver, Kidneys, Intestine, and also the Skeletal Muscles in a binary way, as glucose clients and as part of the global glucose dynamics system-provider/control, in order to investigate possible abnormalities in these functions.

(3) To consider the role of the brain as a primary organ in the control of persistent childhood hyperglycemia should be considered and investigated. We should also look for the sensor neurons that control hyperglycemia, where they are in brain and how and what they operate in this scenario;

(4) To evaluate the implications for childhood hyperglycemia of anomalies in the integrated system of Growth-Cognition-Physical Activities.

(5) To investigate possible glycemic anomalies induced by intense cognition, induced by social media and the media in general, and the role of complex adult information penetrating the children's world causing/inducing anomalous cognition pattern.

(6) To investigate the role in the changes of children's blood glucose level by external noxious elements such as new communication technologies and their radiation [17], heavy metals and persistent pollutants in food and in the air we breathe [73] and persistent stress [16].

(7) To consider and to investigate whether persistent hyperglycemia hyperglycemias induced by any internal or external causes might be pancreas exhaustion for insulin production rather than just its beta cells' death. It means that ceasing pancreas's exhaustion causes might well be that the hyperglycemia will be extinguished/controlled, if the cause is not deleterious.

Items (1) - (7) might be used as a basis for a new paradigm of investigation of persistent childhood hyperglycemia, a new paradigm with more options to provide cure or at least a more humanized and accurate way of treatment for juvenile general hyperglycemia problem or specifically T1DM. Diagnoses and researches based on items (1) - (7) as guide followed in a systematic way and using state-of-the-art medical and technological knowledge will certainly guarantee a cure or an accurate diagnosis for the posed problems, for both non-diabetic hyperglycemia and T1DM. Of course, part of this complex system has already been investigated such as the effects of infections, stress, food intake, HPA axis dynamics, some hypothalamic sensor neurons dysfunctions, on blood glucose homeostasis. However, the glucose homeostasis related literature available nowadays is not systematized in an integrated literature system, several parts of the global body glucose management system (new proposed paradigm) still need systematic research to be integrated into a single and self-consistent system capable of generating a new medical performance via a new medical paradigm accepted and usable by all.

4. Conclusions

T1DM and T2DM are epidemic and must be controlled. The WHO and other

relevant local and international organizations recognize that most of the approaches to access the core principles of T1DM assume it as related to the pancreas failure and its inner dynamics complexity. In this fashion, the specialists on that field try to access the problem using basically biochemistry and biological models of the beta cells life dynamic functioning and death due to immune attacks or other noxious elements [57] [61] [66].

Even if there are in market and described in the related literature a great deal of medicines used to treat T2DM, to T1DM most of what can be seen is the use of insulin in different forms and ways to pump to the body. However, from what can be seen in our work and in the general literature, some of the T2DM medicines could/might, perhaps, be used to mitigate the problem of the persistent infantile hyperglycemia at least the ones that have been misdiagnosed as pancreas failure (T1DM) or worse diagnosed as idiopathic which must have a clear cause that can be accessed with a correct investigation tool. There are clear and real clinical situations where the hyperglycemia is persistent with no observable lack of energy, and no real measurable pancreas beta cells immune attack present, either in image and/or blood and urine analysis (body, blood, and urine indicators). Brain MRI and PET scan, for instance, could be useful tools to consider the brain glucose control system failures as possible precursor of T1DM. And so, in order to treat in a proper way the persistent children hyperglycemia, not just assigning continuously insulin to reduce the glucose blood level, controlling food intake and exercises, what is quite ok and necessary in hyperglycemia regime, however, still, it is necessary a more precise complete and self-consistent diagnosis [67].

We concluded that those well-known failures in diagnosis of T1DM need to be urgently and very deeply addressed, and this is based on our proposed model where we consider the body glucose dynamics as an integrated glycemic system, the coupled four systems presented above. As a consequence, we might find for sure a much better and more human treatment arrangements for so many sick children and real hope for the related families around the world. What clearly cannot be pursued forever, without a proper new diagnosis research paradigm, is just the almost unique insulin-immune problem approach which assigns plenty of insulin to the sick children or that requires other still not well established approaches such as the ones that use stem cells as commonly used nowadays. The stem cells approach it is indeed a hope in the situations where the beta cells were in fact destroyed by noxious attacks [67]-[72]. Of course, in any case, in dark, with known or unknown glycemic anomalies clear causes, the insulin injection externally is a wonderful and highly effective way to maintain the blood glucose at the precise health level until a better solution might be found. The importance of insulin is clearly stated in the summary of the “The Nobel Prize in Physiology or Medicine of 1923”, that was awarded jointly to Frederick Grant Banting and John James Rickard Macleod “for the discovery of insulin”:

<https://www.nobelprize.org/prizes/medicine/1923/summary/>.

Further and very interesting details can be found in “The Discovery of Insulin” by the Canadian Encyclopedia:

<https://www.thecanadianencyclopedia.ca/en/article/the-discovery-of-insulin>.

Finally, what could probably also be argued, after all the considerations in this paper, is that if it could be possible one day to control the excess of the endogenous glucose production by liver, kidney, or skeletal muscles, somehow, when this would be the case, of course, by drugs or something else like the one used to control the cholesterol excess production by liver or metformin for T2DM which is known to exert its anti-hyperglycemic action primarily through lowering of hepatic glucose production (HGP) (Alpha-glucosidase inhibitors as known in literature lower blood glucose by modifying the intestinal absorption of carbohydrates.) [74]. This could for sure protect a health pancreas from exhaustion due to much work to cope the excess of glucose production, assuming a health pancreas with good quality insulin and normal glucagon production, but under a decontrolled endogenous glucose production regime and consequently inducing the pancreas to be not able to deal with the net amount of insulin required to keep the euglycemia under constant glycemia fluctuations.. This decontrol can be by any known reason such as persistent stress and/or intense persistent cognition or even by an idiopathic reason. This could be an alternative to the use of insulin in a case where the hyperglycemia is associated to the excess of endogenous glucose production and not due to pancreas’s beta cell destruction. In this scenario, it could maybe be easier to the parents to control the children medicine intake and its general use, since this control is known as of great deal of physical and psychological stress to the families involved with this disease/body dysfunction.

The main limitation of the proposed model, where we consider the human glycemic system as coupled (internally and externally) and not just the simple uncoupled systems approach, is that to work properly it is to find specialists to be able to understand all parts of the system and their dynamics and not only part of it. In order to do that, in a competent way, those specialists cannot be of only one speciality such as endocrinologist, for instance, or a pure neurologist, or nephrologist, or even a psychiatrist. To study the body glucose integrated management system, it is necessary “to couple” different medical specialities, such as neurology to endocrinology giving birth to the neuroendocrinology, a neuroendocrinologist can understand much better the dynamics of the glucose neuron sensors than a pure endocrinologist. If we couple areas such as endocrinology with neurology and psychiatry, one could better understand how external noxious elements could affect the juvenile glycemic dynamics. Also, if we couple endocrinology with nephrology, we could really understand how kidney interacts with liver in controlling or helping to control the glycemia. Of course, if we couple all those specialities in one element, we could then, indeed, with no caveat, fully access the human body glucose management system in all its strength. Therefore, if there is any limitation in our proposal this is the one; to find researches with this integrated speciality system boarded. Another important issue

to be addressed that induces complications on accessing this topic is how we couple environmental impacts on the homeostasis dynamics by, for instance, hypothesizing that the pollution adversely affects insulin sensitivity and secretion [73]. To model the interaction of Electromagnetic Field (EMF) with brain is also of paramount importance for a wired society due to the intense use of mobile phone, wireless equipments, and internet of things which is a technology that allows people to add a device to an inert object such as vehicles controlling them through a communications network, and so EMF are continuously generated and absorbed by people and things. There are already preliminary studies on how EMF might impact brain generating disease such the very early onset of Alzheimer's Disease [75]. How it impacts the glucose blood dynamics inducing, maybe, hyperglycemia in children and youth in general must be investigated further [17]. Besides, we can add that the human Electromagnetic Hypersensitivity (EHS) is a real health concern and the WHO (World Health Organization) has already documented this further [76] [77].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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