

Diabetes Mellitus: Disorder of Cellular Dysfunction Due to Lack of Entry into Cell of Glucose. The Most Efficient Fuel for Cellular Function*

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Abstract

Background: Diabetes Mellitus is established to be a chronic hyperglycemic disorder secondary to altered glucose metabolism. Alternatively, hyperglycemia may be one of several manifestations in subjects with type 1 and type 2 diabetes Mellitus. Most tissues require insulin for entry of glucose, exceptions being red blood cells, renal medulla and nervous system. Hyperglycemia in intravascular compartment and other extra cellular milieu may be attributed to impaired glucose entry into endothelial cells of the vessel wall and cells in other tissues due to absence of insulin in type 1 and both insulin resistance and decline in insulin secretion in type 2 Diabetes. **Objective:** Hypothesis is proposed that Diabetes mellitus is a disorder of cellular dysfunction due to lack of entry of glucose, the most efficient fuel. Literature review was conducted to establish the perspective. **Results:** Declines in both phases of insulin secretion are induced by lack of glucose entry into pancreatic beta cells. Hyperglycemia is perpetuated by increased hepatic glucose production caused by sustained hyperglucagonemia secondary to lack of glucose entry into the pancreatic alpha cells. Moreover, decline in insulin secretion by beta cells and rise in glucagon release by alpha cells are enhanced by fall in GLP1 and GIP caused by dysfunction of L cells and K cells secondary to lack of glucose entry in both types of diabetes. Increased prevalence of infections and thromboembolic events may be attributed to dysfunction of leukocytes and platelets due to impaired glucose entry. Finally, alterations in metabolemics including Adiponectin, TNF alpha, Plasminogen inhibitor factor 1, Homocysteine, CRP, Lipids etc. as

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well as dysfunction of several organs in both types of diabetes may also be attributed to the lack of glucose entry into specific cells. Hypothesis is validated by improvement in metaboleemics and organ function on facilitation of glucose entry into cells by insulin administration and/or improvement in insulin sensitivity. **Conclusion:** Diabetes mellitus is a disorder manifesting dysfunction involving almost all organs and cells induced by lack of entry of glucose, the most efficient substrate for cellular function.

Keywords

Diabetes Mellitus, Cellular Dysfunction, Cellular Glucose Entry

1. Introduction

Traditionally, diabetes Mellitus has been deemed to be a chronic hyperglycemic disorder secondary to altered glucose metabolism [1]. Alternatively, hyperglycemia may be one of several manifestations in subjects with type 1 and type 2 diabetes Mellitus [1]-[6]. Almost all tissues require insulin for entry of glucose, the possible exceptions being red blood cells, renal medulla, lens as well as central and peripheral nervous systems. However, some recent studies have documented the role of insulin in glucose uptake by the brain and other nervous tissues [1]-[6]. Thus, hyperglycemia in extra cellular milieu including intravascular compartment may be attributed to impaired glucose entry into all cells including hepatocytes, myocytes and adipocytes and even endothelial cells of the vessel wall due to absence of insulin in type 1 and both the insulin resistance and the decline in insulin secretion in type 2 Diabetes [6] [7] [8][9] [10].

2. Pancreatic Dysfunction

In subjects with both type 1 and type 2 diabetes as well as Prediabetes, post prandial hyperglycemia is the initial manifestation induced by the decline in the 1st phase insulin secretion due to inhibited release of stored insulin [7] [11] [12] [13] [14]. Overall diurnal hyperglycemia is further exacerbated later by a marked rise in the inter meal and fasting hyperglycemia caused by the lowering of 2nd phase insulin release [11] [12] [13] [14]. Albeit, the declines in both phases of insulin secretion in type 2 diabetes are induced by lack of glucose entry into pancreatic beta cells as a result of insulin resistance at the beta cells themselves [11] [12] [13]. Finally, progressive beta cell failure described as a natural course of type 2 diabetes is apparently neither universal nor total and therefore may be limited to subjects not attaining and maintaining desirable glycemic control [14]-[24]. Moreover, recent studies have documented that beta cell failure is reversible and preventable by sustained glycemic control [21] [22] [23] [24]. Finally another study recently demonstrated differentiation of beta cells into empty cells devoid of insulin secretory granules in subjects with type 2 diabetes with persistent lapse of glycemic control [16]. Therefore, these findings may be con-

sistent with the reported gradually declining beta cell function which may be attributed to persistent lack of glucose entry into beta cells. Similar progression in type 1 diabetes may be attributed to the same pathophysiology induced by declining circulating insulin due to autoimmune destruction of beta cells.

Sustained circulating hyperglucagonemia ensues due to the lack of glucose entry into pancreatic alpha cells rendering them incapable of recognition of circulating hyperglycemia [25]-[31]. Elevated circulating glucagon in turn promotes hepatic glucose production via glycogenolysis and gluconeogenesis with consequential exacerbation of diurnal hyperglycemia.

Alternatively, the decline in insulin secretion by the beta cells and the rise in glucagon release by the alpha cells is also induced by the fall in Incretins namely GLP1 and GIP caused by dysfunction of L cells in the duodenum and K cells in ileum respectively [32] [33] [34] [35] [36]. The decline in incretin effect may be secondary to lack of glucose entry into these cells due to absence of insulin in type 1 and both the insulin resistance as well as decreased insulin secretion in type 2 diabetes. Alternatively, increased DPP4 activity documented in both type 1 and type 2 diabetes may be responsible for enhanced degradation of Incretins and exacerbate the decline in their circulating levels [37] [38]. The hypothesis is also consistent with available data in literature documenting lowering of plasma glucagon and rise in insulin directly as well as via increase in GLP1 and GIP concentrations on improvement in insulin sensitivity following treatment with insulin sensitizers e.g. metformin or glitazones in type 2 diabetes and by insulin administration in both type 1 and type 2 diabetes [39]-[47]. Finally, alteration of other pancreatic hormones, e. g. amylin, pancreastatin, somatostatin as well as pancreatic polypeptide are documented in both type 1 and type 2 diabetes and may be secondary to dysfunction of other pancreatic endocrine cells due to lack of glucose entry by the same aforementioned mechanism [48] [49] [50]. Finally, hyperglucagonemia occurs despite euglycemia in several disorders and states associated with insulin resistance and may be attributed to inhibited glucose entry into alpha cells [25].

The hypothesis may be extended to dysfunction of the exocrine pancreas since serum pancreatic amylase and lipase concentrations are frequently elevated in subjects with acute lapse of glycemic control, especially diabetic Ketoacidosis and hyperglycemic hyperosmolar nonketotic state [51] [52]. Similarly, more frequent occurrence of pancreatitis, often without a ductal calculus may be secondary to lack of glucose entry into ductal cells as well as the cells of the ampulla of Vater respectively. Finally, greater prevalence of pancreatic maldigestion in subjects with diabetes of both types may attributed to the same pathophysiology [53] [54] [55] [56].

3. Hepatic Dysfunction

Elevations in serum concentrations of liver enzymes especially transaminases are a frequent finding in subjects with diabetes as well as prediabetes attributed to nonalcoholic steatohepatitis [NASH] or “fatty liver” [57] [58] [59]. The patho-

physiology of “fatty liver” in these disorders is well defined. Hepatic conversion of very low density lipoprotein [VLDL] into low density lipoprotein [LDL] is promoted by insulin sensitive hepatic lipoprotein lipase or triglyceride hydrolyase. Therefore, this pathway is inhibited in both type 1 and type 2 diabetes due lack of adequate circulating insulin or presence of insulin resistance leading to rise in serum triglycerides, the major constituent of VLDL cholesterol fraction. Alternatively, lack of circulating insulin or insulin resistance promotes tissue lipolysis with excessive accumulation of free fatty acids in the circulation, the substrate for hepatic triglyceride synthesis. A portion of the increased hepatic triglycerides leaks into circulation and contributes to further elevation of serum concentration while the remnant is stored in the hepatic parenchyma leading to fatty liver or NASH [57] [58] [59]. This pathophysiology of NASH is confirmed by resolution of NASH following insulin administration in subjects with both type 1 and type 2 diabetes as well as insulin secretagogues and insulin sensitizers in population with both prediabetes and type 2 diabetes [57]-[69].

The rise in cytokines; interleukins and C reactive protein in presence of inflammation and infection, the rise in fibrinogen, plasminogen activation inhibitor [PAI] 1 promoting platelet aggregation and coagulation as well as the increase in other Metaboleemics including uric acid, homocysteine Hepatocyte nuclear factor, resistin, growth factors etc. may be secondary to hepatocellular dysfunction induced by the lack of glucose entry into hepatocytes [70]-[75]. Improvement in serum concentrations of these metabolites following administration of insulin sensitizers and/or insulin secretagogues and/or insulin itself in subjects with type 2 diabetes and Prediabetes further enhance this hypothesis [76] [77] [78] [79]. Finally, alterations in several other metabolites in both type 1 and type 2 diabetes may also be attributed to the lack of glucose entry into specific cells generating these metabolites and this pathophysiology is confirmed by reversal towards normalization following promoting glucose entry into these cells by appropriate therapies [70]-[79].

4. Dysfunction of Adipocytes

Until recently, adipose tissue was labeled as a storage organ. However, several recent studies have established adipose tissue to an endocrine organ since it synthesizes and releases several humoral factors recognized as adipokines [80]-[95]. These include leptin, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin as well as other cytokines, e.g. fibroblast growth factor 21 [FGF21], retinol-binding protein 4 [RBP4], dipeptidyl peptidase 4 [DPP-4], bone morphogenetic proteins, [BMP-4 and BMP-7], vaspin, apelin, and progranulin, spexin etc. Secretion of adipokines is altered due to adipose tissue dysfunction and may contribute to a spectrum of obesity-associated diseases including Prediabetes and type 2 diabetes [81] [82] [86]-[91]. We postulate that adipose tissue dysfunction in both Prediabetes and type 2 diabetes is caused by lack of entry of glucose into adipo-

cytes secondary to insulin resistance since similar alterations in adipokines are documented in type 1 diabetes probably by the same mechanism due to lack of circulating insulin [84] [85]. However, the changes in adipokines were dissimilar in comparison to type 2 diabetes as noted by a rise in circulating adiponectin and leptin concentrations at onset of type 1 diabetes followed by a fall with increasing duration of the disorder. Increase at the onset may be attributed to enhanced entry of glucose into adipocytes secondary to insulin hypersensitivity in presence of residual beta cell function. Ensuring fall in adipokines with increasing duration of the disorder appears to be induced by lack of entry of glucose into adipocytes due declining insulin sensitivity and absence of circulating insulin due to progressive destruction of beta cells [84] [85]. The hypothesis is further established by rise in adipokines by blunting of insulin resistance in insulin resistant states and administration of insulin in type 1 diabetes [92] [93] [94] [95].

5. Blood Corpuscular Dysfunction

Increase in both the infection rates and thromboembolic events in hospitalized subjects with hyperglycemia even in the absence of the diagnosis of Diabetes and the improvement in outcomes following a prompt treatment with insulin infusion have been well documented [96]-[104]. Similarly, ambulatory subjects with both type 1 and type 2 diabetes with persistent hyperglycemia are predisposed to recurrent infections, macro vascular outcomes including thromboembolic events as well as microvascular complications [96]-[103] [105] [106]. Increased infections may be attributed to decreased phagocytosis due to dysfunction of white blood cells secondary to lack of entry of glucose induced by insulin resistance and a relative decline or total lack in circulating insulin in both the hospitalized subjects with hyperglycemia as well as ambulatory population with type 2 and type 1 diabetes respectively. The dysfunction of platelets due to lack of glucose entry may be responsible for their enhanced aggregability promoting increase prevalence of thromboembolic events. Adverse macro vascular outcomes are further facilitated by increase viscosity induced by hyperglycemia and its consequential dehydration as well as increased circulating triglycerides [107] [108] [109].

6. Muscular Dysfunction

Lack of glucose entry results in voluntary muscle wasting, weakness and serum irisin with hyperglycemia in subjects with diabetes of both types followed by a recovery and reversal to normal function on attaining and maintaining Glycemic control [110]-[115]. Similarly, involvement of muscles of viscera and their respective sphincters lead to several systemic disorders including [1] GI Tract: Dysphagia, Gastroparesis, Enteropathy, [2] Genitourinary Tract: Retrograde Ejaculation and Erectile Dysfunction in men as well as Dyspareunia and Lack of Orgasm in women [116] [117] [118] [119]. Finally, persistent hyperglycemia due

to lack of glucose entry leads to dysfunction of cardiomyocytes resulting in both Acute Coronary Syndrome as well as cardiomyopathy [119]. Higher the plasma glucose, larger is the size of infarction with increasing mortality as well as morbidity e.g congestive heart failure, cardiogenic shock resulting in longer hospital stay and greater costs [104]. Recent studies have demonstrated improvement in all endpoints by continuous Insulin infusion promoting enhanced Glucose entry into myocardial cells [104].

7. Pulmonary Dysfunction

Decline In Lung Volumes, FEV1, FVC and Diffusion capacity ensue with aging as well as in obese subjects with further exaggeration in presence of diabetes leading to worsening restrictive pulmonary disease frequently resulting in onset of Cor pulmonale [120] [121] [122] [123] These manifestations may be attributed to unifying mechanism; lack of entry of Glucose into alveolar cells and respiratory Muscles of Chest, Diaphragm secondary to insulin resistance as well as a relative or absolute decline in insulin secretion [104].

8. Bone Disorder

Osteocytes require glucose as a fuel for optimal function. Bone mineral density declines with aging, obesity as well as persistent hyperglycemia in subjects with diabetes [124]-[129]. Multiple pathophysiologic mechanisms appear to play a role. Insulin resistance as well as deficiency activate osteoclasts promoting bone resorption. Concurrently, inhibition of osteoblasts ensues decreasing compensatory bone formation resulting in osteoporosis. Moreover, rising concentrations of counter regulatory hormones, e.g., glucagon, cortisol etc. induce decline in matrix via promoting gluconeogenesis from collagen also resulting in osteoporosis. Alternatively, hypercortisolemia also directly facilitates osteoporosis as well as osteomalacia due to decline in circulating active 125 OH vitamin D via inhibition of hepatic 25 hydroxylase. Finally, increased urinary excretion of calcium and phosphate leads to rise in PTH exacerbating bone resorption. Therefore, osteoporosis is a frequent sequel of both type 1 and 2 diabetes secondary to impaired entry of glucose into osteocytes due to lack of insulin and insulin resistance respectively. Improvement in bone mineral density ensues following attaining and maintaining Glycemic control [128] [129] [130] [131] [132].

9. Hypothalamic Pituitary Dysfunction

Inappropriately high serum concentrations of human growth hormone and ACTH are well documented to occur in presence of uncontrolled hyperglycemia e.g. Diabetic ketoacidosis and hyperosmolar state in both type 1 and type 2 diabetes [133]-[139]. The disruption of feedback regulation between glucose and HGH as well as ACTH secretion is accompanied by inhibitions of both hypothalamic Pituitary gonadal and thyroid axes [140]-[152]. Finally, Pituitary dependent endocrine glands fail to function appropriately as well resulting in altered circulating

concentrations of hormones synthesized and secreted by these glands with consequential rise in cortisol and declines in thyroid and gonadal hormones [137]-[153]. These aberrations may be attributed to lack of glucose entry into hypothalamus and various Pituitary cells as well as Pituitary dependent endocrine cells induced by insulin deficiency in type 1 and insulin resistance in type 2 diabetes. Furthermore, thyroid hormonal changes in various “Euthyroid Sick States” and gonadal dysfunction in PCOS and obese subjects are also attributed to insulin resistance at the level of thyroid gland as well as hormonal metabolism in peripheral tissues as well as on the part of ovarian theca cells respectively [147] [154]-[163]. Alternatively, metabolemic changes in several chronic disorders including HIV syndrome, chronic renal failure, malignancy etc. as well as in subjects hospitalized for treatment of acute illnesses may be attributed the same pathphysiologic mechanism [147] [164] [165] [166]. I believe that this pathophysiological hypothesis is confirmed by normalization of function of these hypothalamic Pituitary axes and Pituitary dependent endocrine cells in response to timely improvement in Glycemic milieu following prompt therapy with insulin [104] [162] [163] [167] [168] [169] [170] [171].

Finally, improved outcomes e.g. prompt remission, delay or prevention of recurrences as well as longer survival are reported recently by adjunctive therapy with Metformin or thiazolidinediones in combination with chemotherapy in subjects with various cancers [168] [169] [170]. These benefits may be attributed to enhanced entry of chemotherapeutic agents along with glucose into cancer cells secondary to blunting of insulin resistance present in subjects manifesting cancer. However, a distinct concern exists regarding increased adverse effects induced by entry of chemotherapeutic agent into normal cells.

10. Intravascular Hyperglycemia and Its Consequences

Lack of entry into endothelial cells lining the vessel wall leads both endothelial dysfunction and intravascular hyperglycemia [172]-[178]. Endothelial dysfunction plays a prominent role in exacerbating atherosclerosis in vessels of all sizes resulting in adverse outcomes of both macro vascular and micro vascular variety [169]-[175]. Macro vascular outcomes are further facilitated by increased viscosity induced by dehydration secondary to enhanced diuresis caused by intravascular hyperglycemia. Moreover, intravascular hyperglycemia is responsible for clinical manifestations of diabetes e.g. Polyuria, nocturia, polydipsia, polyphagia etc as well as other acute metabolic aberrations including DKA, Hyperglycemic hyperosmolar state, hypertriglyceridemia etc. Moreover, circulating glucose is metabolized by an alternative polyol pathway with generation of sorbitol by conversion of fructose by aldose reductase [179] [180] [181] [182]. Sorbitol in turn is deposited in various tissues causing other manifestations i.e. blurred vision, acutely and cataracts chronically secondary to deposition in lens; change in mental status secondary to cerebral edema induced by osmotic disequilibrium due to exaggerated entry of glucose into brain; peripheral neuropathy with pa-

raesthesia and hypoesthesia as well autonomic neuropathy with acute orthostasis, gastrectasia, erectile dysfunction etc. caused by deposition in neurilemmal sheaths as well as proteinuria resulting from deposition in renal tubules [179] [180] [181] [182]. Fortunately, all these manifestations are transient and are remitted because this metabolic polyol pathway is reversible following improvement in glycemic control. Moreover, aldose reductase inhibitors prevent or induce a prompt reversal of these complications [182] [183] [184].

Finally, persistent hyperglycemia enhances glycation of multiple proteins also termed as “advanced glycated products” [185]-[190]. Deposition of these products into various organs leads to chronic deadly and often disabling micro vascular complications including nephropathy, neuropathy and retinopathy [17] [18] [19] [20] [185]-[190]. Thus, it is apparent that lack of entry into endothelial cells lining the vessel wall contributes to their dysfunction and results in several adverse outcomes [172]-[178]. Moreover, consequential increased intravascular Glycemic load facilitates other acute manifestations and chronic complications. The hypothesis is further established by improvement in all outcomes by enhancement of entry of glucose into endothelial cells by insulin therapy in both type 1 and type 2 diabetes as well as insulin secretogogs and sensitizers in type 2 diabetes [17] [18] [19] [20] [104] [191]-[203].

In the final analysis, many clinical manifestations, metabolic aberrations and various chronic complications in both type 1 and type 2 diabetes as well as other insulin resistant states may be attributed to dysfunction of cells secondary to inhibited entry of glucose; specific cells requiring insulin for glucose entry. Alternatively, dysfunction of cells not requiring insulin for glucose entry ensues due to excessive accumulation of glucose and contributes to other remaining sequels and metabolic abnormalities. Remission from clinical manifestations and prevention and/ or delay in onset of chronic complications by appropriate therapies in both type 1 and type 2 diabetes and other insulin resistant states enhances the hypothesis.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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