

Changing paradigms in type 2 diabetes mellitus

Romesh Khardori

Department of Medicine, Division of Endocrinology and Metabolism, Strelitz Center for Diabetes, Endocrine and Metabolic Disorders, Eastern Virginia Medical School, Norfolk, VA 23510, USA

ABSTRACT

Diabetes mellitus has been increasing in prevalence and imposes serious economic burdens on both the developed as well as the developing world. Understanding pathobiological underpinning of chronic progressive disease like diabetes is an imperative that we cannot escape. For several decades now, the focus has remained on a two hit theory which begins with insulin resistance and is followed thereafter by the β cell failure. Therapies have revolved around this concept with only limited success. Reorientation in our understanding of "islet pathology" should help rethink strategies that would yield better dividends in terms of effective therapy. Role of Glucagon needs to be revisited and incorporated to create treatment regimens addressing the concept of bi-hormonal defect rather than remaining stuck in standalone "insulinopathy." This brief review hopes to initiate/continue that dialogue.

Key words: β -cell, glucagon, hypothalamus, insulin, islet mass, liver

INTRODUCTION

An estimated 18.8 million adults in the United States are reported to have diabetes mellitus. Diabetes compounds risk for life-threatening micro and macrovascular complications. Studies with intensive glycemic control reveal significant reductions in microvascular complications and possible long-term reductions in macrovascular disease. Several professional organizations (American Diabetes Association, European Association for the Study of Diabetes and American Association of Endocrinologists) have come out with position statements and guidelines regarding management options and goals in treating diabetes. Often these recommendations are driven by evidence supporting the use of a pharmacologic agent based on what is known about the pathogenesis of diabetes and pharmacodynamics of antidiabetic drugs (antihyperglycemic agents) chosen.

A recent survey of goals in U.S diabetes care between 1999 and 2010 showed that almost half of the U.S adults with diabetes did not meet the recommended goals for diabetes care.^[1] While one can assign complex interactions among factors at various levels from patient level to provider and systems level, for difficulty in achieving desired goals, it should not be overlooked that despite best attempts goals may not be achieved because therapy chosen may not address the dominant underlying defect leading to dysglycemia/hyperglycemia.

Key to success in treating disease lies in addressing the defect(s) that drives the pathological process in the first place. This is perfectly demonstrated in the treatment of infections that is driven by identifying the infectious agent responsible for the disease and then choosing appropriate antimicrobial therapy that leads to eradication of infection. Unfortunately in treating metabolic disorders, we are dealing with a chronic disorder, which is often unrelenting and physicians often struggle to contain the damage. Chronic diabetes is no exception to this relentless course at present. It is quite possible that we may have been sidetracked by focusing on factors presumed to have a dominant role in the pathogenesis of diabetes and its complications.

In recent history, diabetes mellitus type 2 has been considered a two hit disorder with insulin resistance playing a primary

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Corresponding Author: Prof. Romesh Khardori, Department of Medicine, Division of Endocrinology and Metabolism, Strelitz Center for Diabetes, Endocrine and Metabolic Disorders, Eastern Virginia Medical School, Norfolk, VA 23510, USA. E-mail: khardoRK@evms.edu

role followed by beta cell dysfunction leading to the clinical syndrome of diabetes with attendant hyperglycemia.

Insulin resistance has been considered the evil force that drives the pathology and therapies have evolved attempting to address this defect with the hopes of improving outcomes. Insulin resistance has been considered to be a driver for pancreatic β cell dysfunction as well based on studies designed to study autocrine effect of insulin on the β cell. There are transgenic rodent models that invoke the need for many of the elements of insulin receptor substrate-2 signaling pathway for proper β cell function and health. This does not necessarily mean that the ligand that drives this system is the insulin itself. Inferences drawn from β cell insulin receptor knock out models, β cell IGF-1 receptor knock out or double knock out models have been recently questioned on technical grounds that these knock outs are unlikely to be β cell specific.^[2,3] It is quite possible that insulin modulation of islet cells/beta cell function is orchestrated at central nervous system (CNS) level or through modulation of other local/regional hormones/transmitters. Indeed fate of beta cell is intricately linked to health of α cell that produces glucagon. α cells are a target for insulin action both through direct and CNS mediated insulin effect resulting in reducing/restraining glucagon secretion by α cells. The α cell specific insulin receptor knock out mouse model manifests glucagon hypersecretion in the postprandial state accompanied by defective glucagon secretion in the fasting state recapitulating abnormalities seen in type 2 diabetes. Interestingly also these animals show expansion of β cell mass indicating an important role for glucagon in regulating β cell mas. The new β cells seem to arise from alpha cells with resultant depletion of alpha cells. Centrally insulin restrains alpha cell glucagon response by acting at the level of ventromedial hypothalamus. The potential for α cell to transdifferentiate into β cell assigns α cell role of guardian for repair and regeneration of injured β cells.

IS INSULIN RESISTANCE THE PRINCIPAL DETERMINANT OF TYPE 2 DIABETES?

This issue is far from settled. Not all patients with insulin resistance have diabetes and insulin resistance alone without β cell insufficiency does not cause diabetes. Most often insulin resistance is accompanied by obesity and hyperinsulinemia. Obesity is often associated with adipocyte dysfunction leading to production a vast number of adipokines/cytokines which adversely impact insulin sensitivity. It could be argued “sick adipocyte” is the cause of insulin resistance rather than its consequence. Certainly insulin resistance places strain on the β cell and

contributes to its dysfunction possibly via glucotoxicity and lipotoxicity leading to hyperglycemia. The notion that insulin resistance is a key determinant of vascular damage in type 2 diabetes also deserves reconsideration in light of adverse outcomes reported with insulin sensitizers (rosiglitazone). Pioglitazone, another insulin sensitizer may not be free from adverse effects particularly in the elderly. This raises an important question that has intrigued clinicians for a long time - that is whether insulin resistance actually offers cardioprotection in patients with type diabetes. A fascinating longitudinal study involving evolution of type 2 diabetes, where the investigator used sophisticated personal omics, dysglycemia was not preceded by insulin resistance.

It is not the intent here to dismiss insulin resistance as a lesser evil; a rich body of literature attests to its important role in evolution of diabetes, what remains questionable is its primacy as the chief instigator.

WHAT ABOUT THE β CELL?

The concept that β cell failure as a consequence of lipotoxicity, glucotoxicity, glucolipotoxicity, oxidative/inflammatory injury or accelerated apoptosis have all been proposed and evidence proffered. Unloading glycemic and lipid load have all been shown to result in improved β cell function even when the peripheral insulin resistance remains unchanged. Furthermore, regardless of the severity of insulin resistance, hyperglycemia does not develop as long as the β cell is functioning appropriately. Consequently, the β cell has come under sharp scrutiny in terms of strategies that would improve its function or prevent/decrease apoptosis. Hyperglycemia that beta cell failure begets further adversely affects the β cell itself as well as other sites (liver, muscle and kidney) contributing to worsening hyperglycemia. Until very recently treatments were mostly geared towards either providing more insulin, augmenting insulin action or coaxing pancreas to produce more insulin. The ensuing hyperinsulinemia which would compound preexisting hyperinsulinemia seen in insulin resistance was considered essentially innocuous. These treatments were not entirely harmless. Studies where insulin or insulin secretagogues were used with the hopes of reducing macrovascular complications by strict glycemic control were disappointing.

Actually questions were raised about the safety of intensified control in patients with type 2 diabetes mellitus and preexisting cardiovascular disease (ACCORD, VADT). Aggressive glucose lowering was shown to be of no benefit in type 2 diabetic patients undergoing cardiovascular

surgery in recently reported NODS study. There was actually a three-fold higher risk for stroke.^[4]

Focus on β cell and its products (mostly insulin) and glucose: insulin - glucose axis has possibly hindered considering other potential angles that are relevant to both etiology as well as treatment of diabetes. Attention to this was very tastefully articulated by late Denis McGarry in his article "What if Minkowski had been ageusic..."^[5] He argued that hyperglycemia and insulin resistance might be better explained when viewed in the context of underlying abnormalities in lipid metabolism.

In recent years, many systems have been uncovered that regulate β cell mass and function. Knowledge gained from these investigations raise hope for developing alternate forms of therapeutic regimen that would prevent β cell loss and possible enhance its action. A more recent discovery that has somewhat caused a flutter is the trans differentiation of β cell to α cell in patients with type 2 diabetes which might explain progressive worsening of hyperglycemia in patients with diabetes. It is proposed that dedifferentiation trumps the endocrine cell death in the natural history of type 2 diabetes. Salvaging this dedifferentiation process might be an approach to treating β cell dysfunction in diabetes.^[6] Conversion of mature human β cell into glucagon producing α cell can happen without any genetic modification.^[7]

Is β cell alone the Holy Grail in fuel metabolism/dysmetabolism?

Review of evidence gathered over last 4 decades would argue that insulin centric view of metabolic homeostasis is incomplete and that glucagon is the other key regulator of normal fuel metabolism. Glucagon is the product of α cell that lies in the immediate neighborhood of β cell. Their proximity to each other argues for a mutual paracrine control. In type 1 diabetes, mellitus (T1DM) most of the abnormalities associated with insulinopenia can be eliminated by glucagon suppression. Somatostatin alone was able to treat diabetic ketoacidosis without any need for insulin.^[8] Administration of recombinant leptin to insulin - deficient mice with uncontrolled T1DM reversed entire catabolic syndrome without replacement of any insulin.^[9] However, in intact subjects the function of suppressing glucagon secretion rests with insulin. Thus while insulin alone may not be the sole factor in regulating glucose metabolism, it is an important adjunct that exerts critical restraint over the cell. Therefore, in situations where the β cell becomes sick/inefficient/dysfunctional, α cells secretory product - glucagon makes matters worse. Thus, our focus on substituting insulin alone may not be sufficient since we may not be able to achieve safely insulin

concentrations within islets that are necessary for glucagon suppression.

Until recently glucagon's primary action was limited to the liver where it augments hepatic glucose output. Recently, it was shown that glucagon has an opposing action on liver (suppressing hepatic glucose output) brought about by acting through mediobasal hypothalamic region of the brain.^[10] High fat diet appears to induce resistance to this negative feedback loop contributing further to worsening hyperglycemia seen in obesity, diabetes or both.

Reviewing evidence from various experimental models such as glucagon receptor knockout mice (GlcR $-/-$), Arx deficient mice, studies with noninsulin glucagon suppressors (Amylin, GLP-1 agonists), a persuasive case be made for the crucial role of dysregulated glucagon secretion in type 2 diabetes and beneficial effects from its amelioration.

New pathogenetic paradigm

It incorporates both cell types of pancreatic islet operating in a reciprocal fashion, operating via a loop that includes liver and the CNS. While insulin operates outside this loop as well, glucagon's sphere of activity largely rests within this loop. Despite the appreciation of benefits of lowering glucagon secretion in hyperglycemic states, long-term effects of reduced glucagon signaling remain a concern. It must be appreciated as well that glucagon is the principal defender against hypoglycemia and blunting/abrogating glucagon signal might adversely impact recovery from hypoglycemia - a major concern in people with diabetes.

Need to reconsider ways to mitigate insulin - glucagon dissonance stems from failure of insulin alone to provide safe effective control of diabetes in patients with long standing diabetes particularly in those with vascular complications. Furthermore, it is influenced by the recent discovery that hyperinsulinemia, often written off as benign consequence of insulin resistance, may not be that benign. Recent experiments in mice creating Ins-1 haploinsufficiency lead to protection from diet induced obesity and reprogrammed white adipose tissue to express uncoupling protein 1 and increase energy expenditure.^[11] These observations would support the conclusion that hyperinsulinemia may actually contribute to expansion of fat mass that would then add all metabolic dimensions that one encounters in obese patients. In addition, treating insulin resistance with insulin at higher doses may be deleterious for tissues where insulin resistance may actually be offering protection against metabolic stress.^[12] Alternative therapies, which target glucagon hypersecretion may be more appropriate under these circumstances.

SUMMARY

Type 2 diabetes is an increasing global problem. Oral antihyperglycemic agents alone often fail to bring patients to target goals and use of insulin might not always be a safe option. Awareness of perturbations in the cell secretion and its correction deserves more scrutiny. Future therapies should be directed at countering effects of glucagon at the hepatic level without countering its central role at the CNS level. At present it remains a concept, but nothing stands in a way of exploring this possibility. Such therapies must be safe and free from any worrisome adverse effects (cellular hyperplasia, adverse hepatic effects etc.). There is a dire need to avoid the use of insulin beyond limits of safety.

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