Abstract
Advances in our understanding of the pathophysiology have spurred improvements in the way we approach and manage the disease. From being considered a disease of insulin deficiency, to one of insulin resistance (mediated by the liver, muscle and fat cell) and deficiency combined, to the multifaceted syndrome we now know it to be, diabetes has evolved significantly. This review describes the recently identified mechanisms linked with the causation and development of diabetes. It includes the newer players listed in the Ominous Octet (the alpha cell, the gastrointestinal tract, kidney and brain) and describes four hormones which complete the Dirty Dozen (dopamine, testosterone, renin-angiotensin system, Vitamin D). The article goes on to discuss fresh research incriminating iron and gut-derived serotonin in the etiopathogenesis of diabetes, and suggests therapeutic implications of pathophysiologic advances.

Keywords: Pathophysiology, Insulin deficiency, Multifaceted syndrome.

Introduction
Occam’s razor, a traditional pedagogic tool, is often used in medical education, to find a single cause for a multitude of symptoms and signs. Diabetes, however, is an ambassador for the anti-razor philosophy. A single disease, with multiple etiologies and associations, diabetes continues to reveal its hidden facets one by one.

The last decade has seen a multitude of newer drugs and modalities for diabetes management, matching the explosion in the diabetes pandemic. Few of us, however, realize that drug development for a disease follows advances in our understanding of its pathophysiology. Effective management of any disorder is possible only if it is based on an in-depth understanding of its etiopathology. It is pathophysiology which informs our choice of pharmacology, not the other way round. This review highlights recent advances in our knowledge of diabetes.

The Beta Cell:
In the traditional gluco-centric approach to diabetes, the beta cell is thought to be the seat of diabetes pathophysiology. Within the beta cell, however, newer discoveries have been made regarding the dysfunction of the beta cell. Age and genes (the T-allele of single nucleotide polymorphism rs7903146 of the TCF7L2 gene, for example) are two non-modifiable factors which influence beta cell health. Insulin resistance, lipotoxicity, glucotoxicity, and incretin defects, are four factors, however, which can be modified to improve beta cell function.1 Hypersecretion of islet amyloid polypeptide (IAPP), which is co-secreted with insulin, can lead to progressive β-cell failure as well. The now discontinued rosiglitazone has been shown to protect human islets against IAPP toxicity by a phosphatidylinositol (PI) 3-kinase-dependent pathway.2

Insulin Resistance:
Insulin resistance, apart from insulin deficiency, plays a pivotal role in the natural history of diabetes. Resistance is mediated at the level of three organs - liver, adipose tissue, and muscle. This trio contributes much more than mere insulin resistance, however, to the biochemical potpourri of diabetes.

The Liver:
In fasting conditions, glucose is produced by the liver. While a non-diabetic individual’s liver produces 2 mg/kg/minute of glucose, a diabetic liver releases 2.5mg/kg/minute. This burdens the circulation with an extra 25-30 g of glucose everyday night, and causes fasting hyperglycemia. Apart from insulin resistance, hyperglucagonemia, increased hepatic sensitivity to glucagon, lipotoxicity, and glucotoxicity all enhance hepatic gluconeogenesis.1 In spite of detailed characterization of the hepatic contribution to diabetes, few molecules target this metabolic defect. Metformin, and the glucagon-like peptide 1 (GLP1) agonists liraglutide and exenatide suppress hepatic gluconeogenesis.

Muscle:
The diabetic muscle is a major site of insulin resistance
and may account for over 85-90% of impairment in total body glucose uptake. Multiple intramyocellular defects in insulin action have been discovered, including impairment of glucose transport, glucose phosphorylation, glycogenesis, and glucose oxidation. These defects are mediated by dysfunction of the insulin signaling pathway at the IRS-1 (insulin receptors substrate-1) and mitogen-activated protein (MAP) kinase levels. Of all drugs for diabetes, only glitazones simultaneously augment insulin signaling through IRS-1, and inhibit MAP Kinase pathways.3

The Fat Cell:
Ample evidence proves the role of fat cell physiology and anatomy in the pathogenesis of type 2 diabetes. Insulin has an anti-lipolytic effect, to which diabetic fat cells are resistant. In such cases, sustained lipolysis increases plasma free fatty acid levels, stimulates gluconeogenesis, causes insulin resistance, and impairs beta cell function (lipotoxicity). Fat cells produce more pro-inflammatory cytokines (leptin), and lesser anti-inflammatory cytokines (adiponectin) in diabetes, contributing to metabolic dysfunction. Larger-sized fat cells have less capacity to store fat, and lipid therefore overflows into muscle, liver, beta cells, and arterial vascular smooth muscle cells.1 Pioglitazone is one drug which has beneficial effects on fat cell economy,1 and its prudent use in diabetes should be encouraged.

The Ominous Octet:
While clinicians and researchers have been aware of the beta cell and the insulin resistant troika for the past few decades, recent findings have brought other organ-systems to center stage. De Fronzo has used the term “Ominous Octet” to describe these players of the diabetology orchestra.1

The Alpha Cell:
Earlier considered the Cinderella of the pancreatic islet of Langerhans, the contribution of hyperglucagonemia to fasting hyperglycemia in type 2 diabetes is well accepted now. Glucagon stimulates hepatic gluconeogenesis and thus contributes to worsening of diabetes. Currently available glucagon-like peptide 1 (GLP1) agonists, such as liraglutide and exenatide, correct this dysfunction. This mechanism, along with others, helps these drugs achieve improvements in glycaemic control, weight, and insulin resistance. Glucagon receptor antagonists are also under development.4

The Gastrointestinal Tract:
The importance of the entero-endocrine axis in the pathophysiology of diabetes is becoming clearer by the day. Deficiency of GLP-1, and resistance to GIP (gastric inhibitory polypeptide), are two defects which contribute to the diabetic milieu, in multiple manners. Two classes of drugs, the GLP-1 agonists, and the dipeptidyl peptidase-4 inhibitors, have been developed to manage diabetes by targeting these defects.5 These include liraglutide, exenatide, sitagliptin, vildagliptin, saxagliptin, and linagliptin.

The Kidney:
The kidney filters about 162g of glucose every day. 90% is reabsorbed by the SGLT2 (sodium glucose transporter 2), located in the convoluted segment of the proximal tubule, and 10% by the SGLT1 transporter in the straight segment of the descending proximal tubule. In type 1 diabetes, the maximal renal tubular reabsorptive capacity for glucose is increased, thus contributing to hyperglycemia.6 SGLT2 inhibitors, such as dapagliflozin and canagliflozin, act by reducing reabsorption of glucose, thus causing glycosuria, but reducing hyperglycemia, in patients with type2 diabetes.7

The Brain:
De Fronzo discusses the concept of insulin resistance in the brain, and notes that hypothalamic centers for appetite regulation are dysfunctional in obese subjects.1 This ‘cerebral insulin resistance’ may lead to increased hepatic glucose production and reduced peripheral glucose uptake. No specific drugs have been developed to counteract this aspect of diabeto-pathophysiology, but leptin, which has hypothalamic effects,8 is being studied as a target for intervention. Insulin detemir, which has weight reducing properties, acts on the hypothalamus as well.9 More recently, the blood-brain barrier has been suggested to be an endocrine organ which secretes various substances which may alter drug function.10

The Dirty Dozen:
Diabetes has much more in store for us, though. Recently, a new moniker has been proposed for a larger etiopathologic group, including four more hormones: the Dirty Dozen.11

Dopamine:
Dopamine, the most abundant catecholamine in the brain, is “the forgotten felon” of diabetes.12 This, along with other catecholamines of the autonomic nervous system, helps modulate glycaemia. Hyperdopaminergism initially evolved as an adaptive mechanism for migrating birds, which needed extra energy. However, a sustained hyperdopaminergic
(hyperadrenergic) state is a maladaptation which may lead to hyperglycemia. Modulation of this condition, using timed release bromocriptine, is a novel means of managing diabetes. Non-pharmacological means of reducing catecholamines, i.e., reducing stress, such as coping skills training and relaxation therapy, are integral to effective diabetes care.

**Vitamin D:**
Vitamin D seems to have found its way into every medical specialty, from psychiatry to dermatology. Actually a hormone, with endocrine, paracrine as well as intracrine activity, Vitamin D is involved in both type 1 and type 2 diabetes mellitus development. Its anti-inflammatory and immuno-modulatory properties protect children against type 1 diabetes, while low levels of vitamin D are associated with a higher risk of metabolic syndrome and its components. The heliophobic habits of South Asians (staying indoors, using sunscreens, and preference for skin covering clothes) do no good to our skeletal and non-skeletal health. While Vitamin D cannot be touted as a cure for type 2 diabetes, supplementation with this hormone has been shown to have multiple beneficial effects.

**Testosterone:**
Hypogonadism is linked, in men, with insulin resistance, and a higher risk of diabetes. This is true for men with congenital hypogonadotropic hypogonadism, as well as men with acquired disease, such as those on androgen deprivation therapy for carcinoma prostate. Androgen replacement improves glycaemic and related metabolic parameters in hypogonadal men, while reducing exogenous insulin requirements. Physicians should screen men with diabetes for hypogonadism, and realize that there is much more to testosterone than sexuality and bone health.

**Renin Angiotensin System (RAS):**
The renin angiotensin system (RAS) was earlier thought to be a metabolic player limited to the blood pressure arena. Recent discoveries related to its circulating as well local (tissue) functions, which mediate endocrine, paracrine, and autocrine effects, have brought RAS to diabetology as well. RAS is present in the beta cell, and cross talk between RAS, insulin, and Vitamin D has been documented. RAS-tropic drugs such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers are drugs of choice in hypertension associated with diabetes.

**The Treacherous Thirteen, The Faithless Fourteen:**
The dirty dozen is not the end of the road for diabetes researchers. Newer associations and etiologies are being uncovered for this colossal disease.

**Iron:**
It may seem surprising to iron-deficient South Asia, but a positive link between high iron (ferritin stores in the body and insulin resistance has been described. Haemochromatosis is associated with 'bronze diabetes'. Increased activity of an iron transporter, called divalent metal transporter 1 (DMT1) protein, has been demonstrated to cause beta cell damage by increasing intracellular iron-levels. This too, may be a potential therapeutic target in selected patients.

**Serotonin:**
Gut-derived serotonin (GDS) has been suggested as a novel cause of hyperglycaemia. The gut secretes serotonin, which in turn activates hormone sensitive lipase to increase lipolysis. It also inhibits glucose uptake into hepatocytes, and increases hepatic gluconeogenesis. By these mechanisms, it contributes to hyperglycaemia. While this is an adaptive response to fasting, it may be maladaptive for diabetes. It is possible that gut-derived serotonin synthesis inhibition will emerge as a new therapeutic target for management of diabetes.

**Conclusion**
The mechanisms of diabetes continue to increase in number. From the dirty dozen to larger, Brobdignagian adjectives, there seems to be no end in sight to the terms used to describe their lists.

What do these multiple defects imply for the clinician? Diabetes is not a single homogenous entity, but a heterogeneous syndrome of metabolic defects, some causative, others associations. Multiple drugs, used in combination, are required to correct diabetes, and one should not rely upon a single class of drugs. Treatment should aim to reverse known pathogenic abnormalities and plan to achieve composite endpoints instead of just glucocentric targets. Therapy must be started early to maintain beta cell health, utilizing insulin sensitizers along with secretagogues. Newer drugs such as gliptins and GLP-1 agonists have an important role to play. Insulin must be used in a timely manner, and the advantages of insulin analogues should be harnessed to provide safety, tolerability and convenience, along with efficacy, to people with diabetes. Further developments in diabetes pharmacology may revolve around the other metabolites discussed above.

As we learn more about diabetes, we hope to develop better modalities for its management, and
ultimately, its cure.

References


