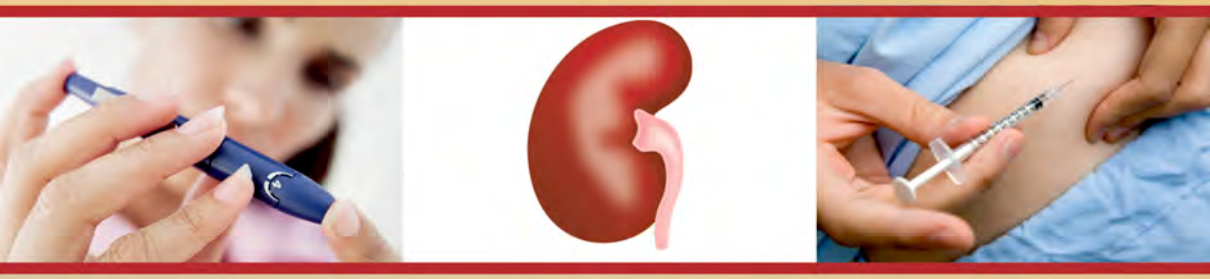
RAJEEV CHAWLA

MANUAL OF
DIABETES CARE



Foreword
SV MADHU

JAYPEE

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Type 2 Diabetes: Etiology and Pathogenesis

Introduction

The pathophysiology of diabetes includes defects in the insulin action or secretion, which leads to glucose intolerance and an eventual progression to full-blown disease. The resistance to action of insulin in muscles or adipose tissue progressively increases causing pancreatic β-cells hyperstimulation to overcome the tissue resistance. This process continues till β cells can compensate for insulin resistance, but eventually the β cells get progressively exhausted leading to corresponding increments in the glucose levels.

Glucose Homeostasis

A discussion on the pathogenesis of type 2 diabetes mellitus (T2DM) must start with a review of mechanisms involved in the maintenance of normal glucose homeostasis in the basal or postabsorptive state. In the postabsorptive state, a majority of the glucose disposal occurs in the tissues, which can utilize glucose independent of insulin. A major portion of this utilization occurs in the brain followed by the uptake in the splanchnic area. The remainder of glucose utilization occurs in insulin-dependent tissues such as muscles and adipose tissue. Basal glucose utilization is matched by the endogenous production of glucose from liver.

The balance between endogenous glucose production and tissue uptake is disrupted following glucose ingestion. There is an increase in the plasma glucose levels, which stimulate the secretion of insulin from the β cells in the pancreas. This then leads to glucose uptake by splanchnic and peripheral tissues as well as suppression of endogenous glucose production from liver (hepatic glucose production).

FAST FACT In the postabsorptive state, a majority of the glucose disposal occurs in the tissues, which can utilize glucose independent of insulin like brain followed by the uptake in the splanchnic area. The remainder of glucose utilization occurs in insulin-dependent tissues such as muscles and adipose tissue.

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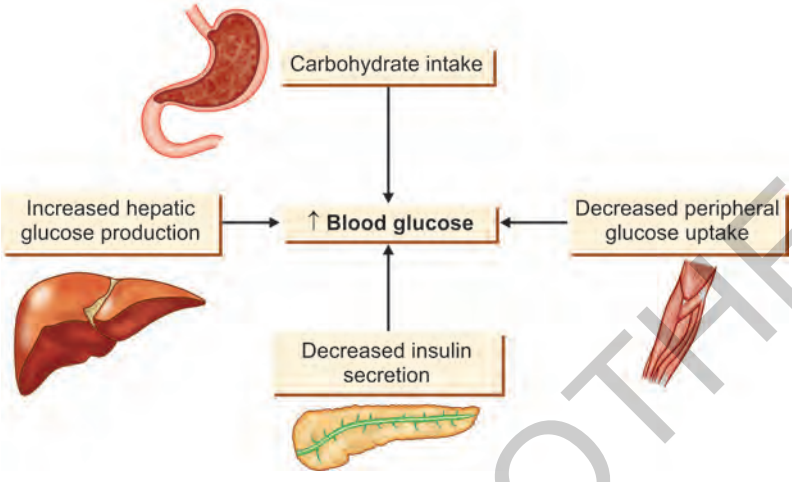
FIGURE 1 Basic pathophysiology of abnormal metabolism of glucose in type 2 diabetes.



Besides this, insulin has a strong inhibitory effect on lipolysis and small increments in insulin levels can lead to a remarkable antilipolytic effect, thereby reducing the plasma free fatty acid levels. This leads to enhanced uptake of glucose in muscle (Fig. 1).

Pathophysiology of Type 2 Diabetes

β-cell Dysfunction

In recent years, it has been observed that β-cell dysfunction plays a major role in the development of type 2 diabetes, across the spectrum of the disease, from prediabetes to diabetes. The β cells are in a constant state of dynamic change, with continued regeneration of islets and simultaneous apoptosis. This delicate balance between islet neogenesis and apoptosis can be disturbed by multiple abnormalities (Fig. 2).

With progressive β-cells failure, there is an inadequate insulin secretion in response to rising blood glucose levels. This worsening β-cells function leads to worsening hyperglycemia and diabetic complications over a period of time (Fig. 3). Environmental factors such as diet, obesity, gender and age contribute to the genetic predisposition leading to an altered glycemic milieu and consequent hyperglycemic state (Fig. 4).

Insulin Resistance

Insulin resistance is a core defect in the pathophysiology of type 2 diabetes. Insulin resistance can be defined as an impaired response to physiological effects of insulin,

FAST FACT Progressive β-cell dysfunction plays a major role in the development of type 2 diabetes, across the spectrum of the disease, from prediabetes to diabetes while insulin resistance remains almost constant.

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FIGURE 2 Factors contributing to β-cell failure in type 2 diabetes.

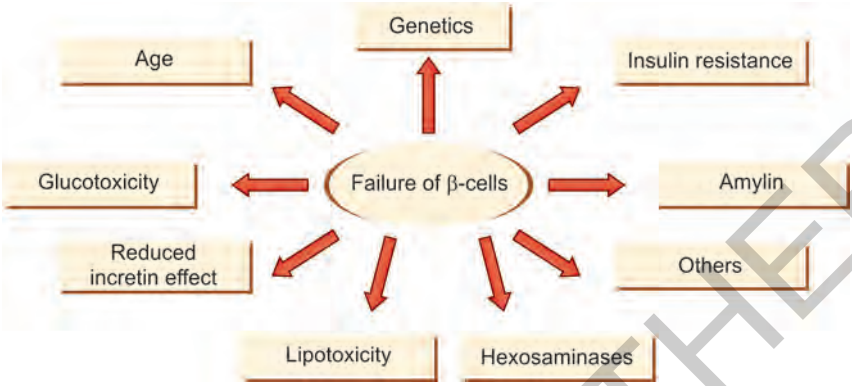
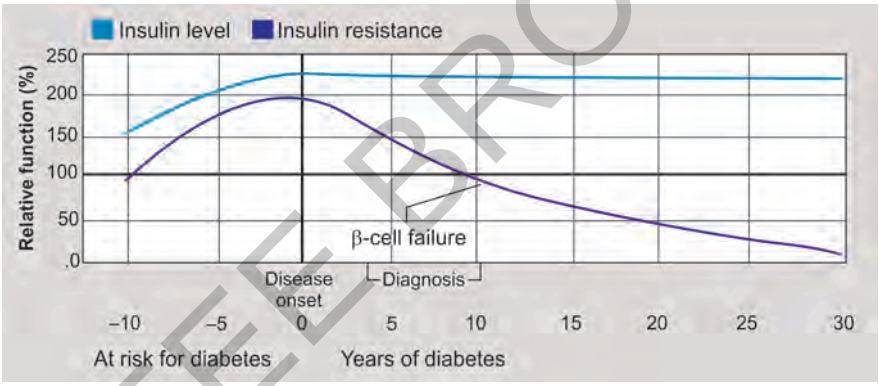


FIGURE 3 Progressive β-cell decline.



Source: Adapted from Bergenstal, et al.

including the effects on glucose, lipid, protein metabolism, and the effects on vascular endothelial function. Insulin resistance, apart from insulin deficiency, plays a key role in the natural history of diabetes. Insulin resistance is mediated at the level of liver, adipose tissue and muscle. However, the triad of factors contribute much more than mere insulin resistance to the biochemical potpourri of diabetes (Fig. 5).

The "Triumvirate"

De Fronzo initially described the combination of insulin resistance in the muscle and liver and the eventual β-cell failure and labeled the combination as "the triumvirate". The insulin

FAST FACT Insulin resistance is a core defect in the pathophysiology of type 2 diabetes which sets in much earlier during the natural course of disease.

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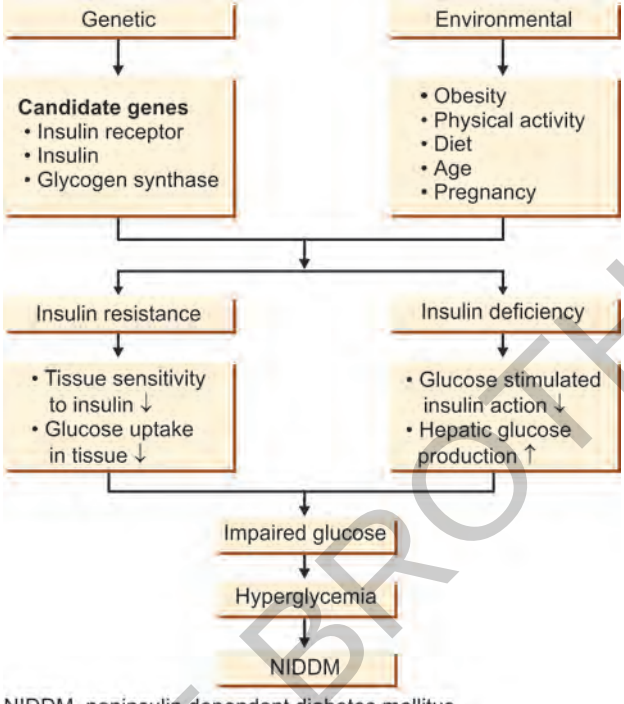
FIGURE 4 How genetic factors and environment interact in type 2 diabetes.



NIDDM, noninsulin dependent diabetes mellitus.

resistance results in hyperglycemia, poor metabolic control, and a further decline in insulin sensitivity; however, disease progression is determined by the progressive β-cell failure.

This results in the natural progression from normoglycemia to impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), which leads to postprandial hyperglycemia and eventually progression to type 2 diabetes. IGT leads to an increased risk of progression to type 2 diabetes and an increased risk for cardiovascular disease (CVD) and death.

Obesity

Presence of obesity and/or lack of physical activity are the principle determinants for the development of insulin resistance. It is considered that a comparatively higher amount of abdominal fat in diabetics than nondiabetics may have a direct effect on the development of insulin resistance and chronic disease. Adiposity also leads to an increased release of proinflammatory cytokines like TNF-α, monocyte chemoattractant protein (MCP-1), and interleukin 6 and 8, which in turn tend to cause a worsening of insulin resistance (Fig.6).

Apart from type 2 diabetes, insulin resistance is associated with the development of a plethora of clinical conditions. These are shown in Figure 7.

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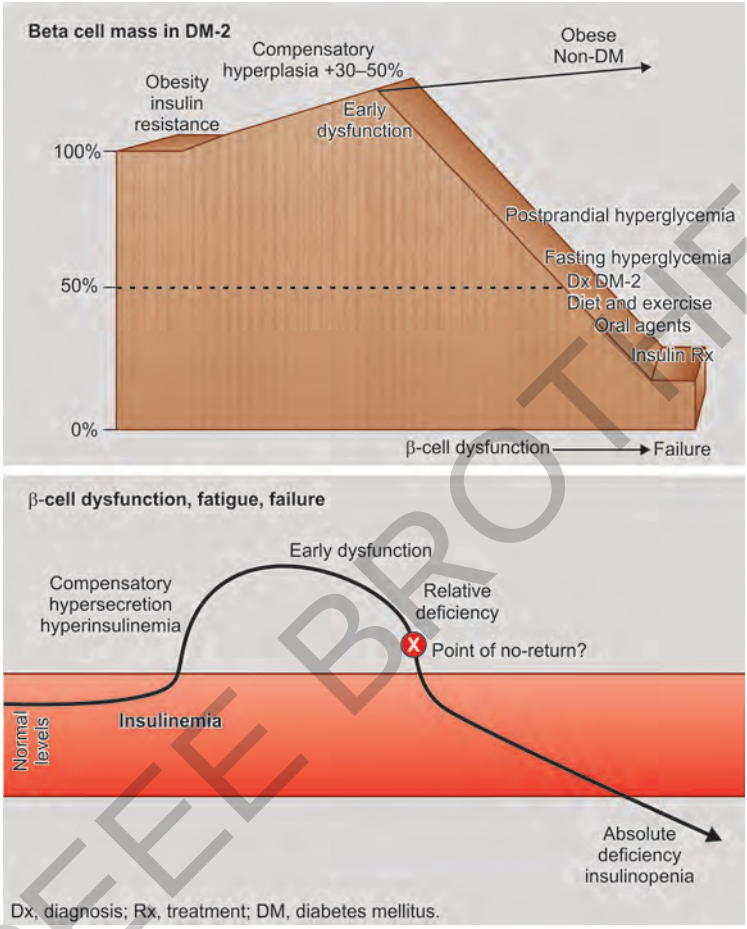
FIGURE 5 **Insulin resistance and β-cell dysfunction lead to type 2 diabetes.**



Genetic Predisposition

Genetic predisposition is another factor in the development of type 2 diabetes. A number of genetic variants have been identified in genome-wide association studies of single-nucleotide polymorphisms (SNPs), and are associated with β-cell dysfunction and insulin resistance. An increased risk for type 2 diabetes has been demonstrated with around 40 independent loci. While there is a wide variation in the prevalence of type 2 diabetes among different ethnic groups, specific populations also have variable environmental and cultural influences, which independently affect the individual's risk of developing the disease (Fig. 8).

It is important, to distinguish between diabetogenic genes and diabetes-related genes that regulate appetite, energy expenditure and intra-abdominal fat accumulation. The latter

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FIGURE 6 **The relation between insulin resistance, obesity and dyslipidemia.**

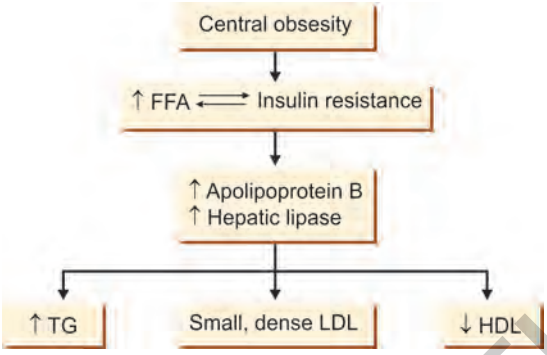


FIGURE 7 **Conditions associated with insulin resistance.**

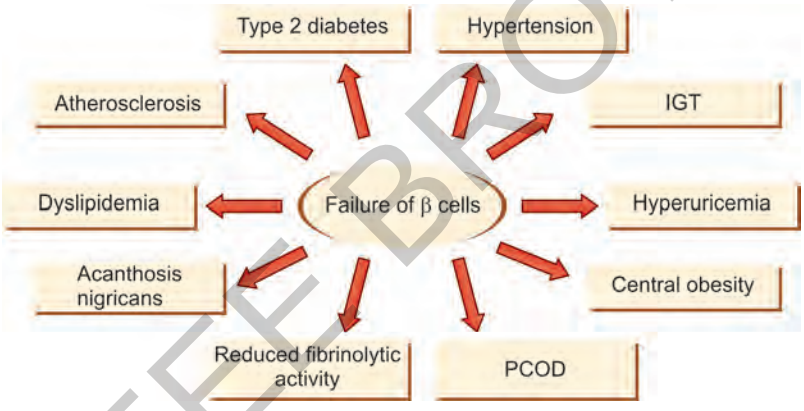
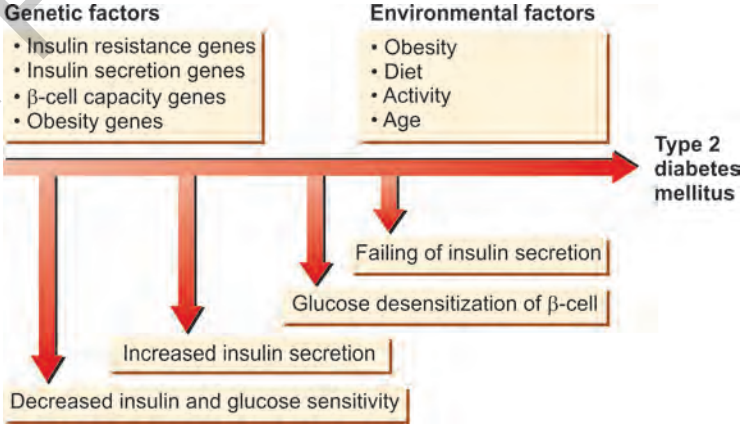


FIGURE 8 **Genetic and environmental factors interact and contribute to the progressive pathophysiology of type 2 diabetes.**



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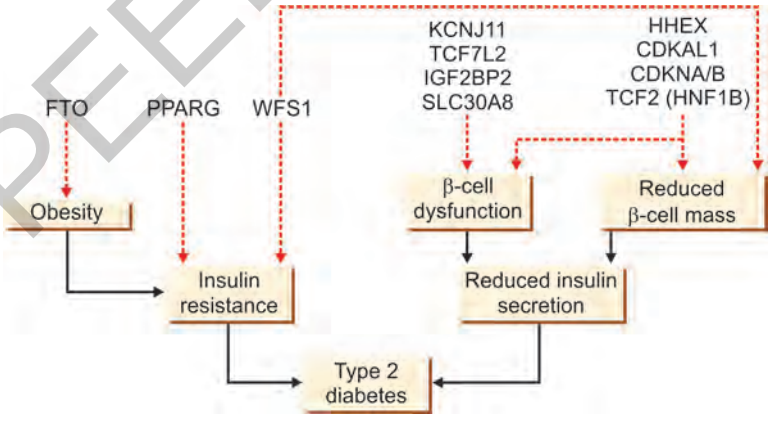
class of genes may be considered as nonspecific and not being mainly limited to diabetics; there by not being sufficient to cause diabetes by themselves. A diabetogenic gene may be defined as being essential and relatively specific but, given the polygenic nature of type 2 diabetes, may not be sufficient in itself to cause diabetes. This would lead us to the observation that a combination of several diabetes-related and diabetic genes may be necessary to cause diabetes and this will be influenced by the severity of the expression of these genes and also by the environmental factors surrounding an individual (Fig. 9).

From the Triumvirate to the Ominous Octet

Over the years we have learned that apart from the established culprits, other factors also contribute to the complex pathogenesis of type 2 diabetes. Apart from the factors described as the triumvirate, many other factors have been found to contribute to the pathophysiology of type 2 diabetes. Defronzo, in his Banting Lecture at the ADA meet in San Francisco described how other factors are also involved in the pathogenesis and described a plethora of other factors labeled as the "ominous octet". This paradigm shift in our knowledge is based upon pathophysiology, which further presents a novel approach to the treatment of type 2 diabetes.

Defronzo described how along with fat cells, gastrointestinal tissues and incretins, pancreatic β-cells, kidneys (absorb up to 90% of the filtered loss of glucose), and the brain, all form a cohort, labeled as the "ominous octet" by him (Fig. 10)

FIGURE 9 **Factors that can genetically predispose to type 2 diabetes.**



FAST FACT There has been a significant advancement in our understanding about pathophysiology of type 2 diabetes from triumvirate to ominous octet.

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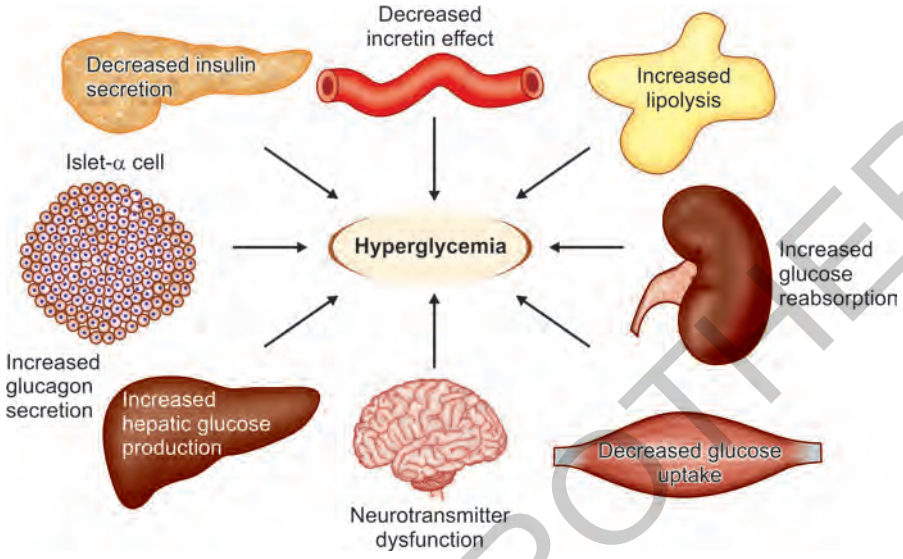
FIGURE 10 **The ominous octet.**



The Dirty Dozen of Diabetes (Proposed by S Kalra, R Chawla, SV Madhu)

However, there were more surprises in store and researchers found that there was more to diabetes than what was previously understood. New factors have been identified, that may contribute to the pathogenesis of T2DM and this led to the new concept of dirty dozen. It is proposed that at least four more factors contribute to the pathophysiology of type 2 diabetes; these include dopamine, vitamin D, renin-angiotensin system (RAS) and testosterone.

Dopamine is a catecholamine with highest concentration in the brain, and was labeled as "the forgotten felon". The autonomic nervous system is also involved in the modulation of glycemia, in addition to the cerebral resistance described by Defronzo. It is known that stress is usually associated with the onset and poor control in diabetes. This could be observed in stress induced hyperglycemia and improves with use of cognitive therapy and coping skills. Extended-release bromocriptine has also been shown to be useful in correcting the hyperdopaminergic state associated with type 2 diabetes in selected patient populations.

Vitamin D acts as an immunomodulatory hormone and restores the cytokine balance by reducing proinflammatory cytokine levels and increasing the anti-inflammatory cytokines.

FAST FACT It is proposed that at least 4 more factors contribute to the pathophysiology of type 2 diabetes; these include dopamine, vitamin D, renin-angiotensin system (RAS), and testosterone making it dirty dozen than ominous octet only.

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Vitamin D supplementation has been found beneficial in both type 1 and 2 diabetic subjects especially in deficient states.

Our understanding of the RAS has evolved and it should be appreciated that it has paracrine and autocrine functions apart from the endocrine effects. RAS is not just present in the vascular system it also exists as local RAS in many organs including the β cell, brain, kidneys etc. The role of RAS is highlighted in the observation from randomized controlled trials demonstrating a lower incidence of new-onset diabetes in subjects receiving angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents.

The last and the twelfth culprit in the series is testosterone. T2DM is shown to be associated with low testosterone in many recent studies. The increase in obesity in diabetes mellitus goes parallel with reduction in testosterone, which leads to reduction in muscle mass hence, inducing severe insulin resistance and a proinflammatory state. It has been found that lower levels of the hormone predate the onset of diabetes; prostate cancer patients who receive androgen-deprivation therapy have a worsening of glycemic status. It is now recommended that diabetic men should be screened for hypogonadism and correction of low testosterone levels should be considered as hypogonadotropic hypogonadism was seen in about 36% of T2 diabetic patients in our own study.

Do We Know Everything?

As we are about to finish the discussion the author would like to highlight the fact that the ominous octet was not the end of the story, the Dirty dozen still have more company. It has been recently postulated that high levels of iron can aggravate insulin resistance in the body. Research has shown that increased activity of the iron transporter, divalent metal transporter1 (DM1) protein can cause β−cell damage by increasing intracellular iron-levels. Furthermore, gut-derived serotonin (GDS) has been postulated as a novel cause of hyperglycemia. Serotonin is secreted in the gut, and it increases lipolysis by activating the hormone sensitive lipase. It also inhibits glucose uptake into hepatocytes, and increases hepatic gluconeogenesis.

Conclusion

While there has been significant advancement in our understanding about pathophysiology of type 2 diabetes, it can be safely assumed that there is still much more than what meets the eyes and the final word is yet to be said. Diabetes is not just restricted to the understanding of insulin and glucagon functioning and their interaction, it is a plethora of multiple metabolic defects that either cause or are associated or aggravate the hyperglycemic state. While new research improves our understanding and newer pathways are discovered, every attempt should be made to translate these into preventive and therapeutic strategies.

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Key Points

We have come a long way as far as our understanding about pathophysiology of type 2 diabetes is concerned starting from Triumvirate to ominous octet to dirty dozen, there is still much more than what meets the eyes and the final word is yet to be said. Diabetes is not just restricted to the understanding of insulin and glucagon functioning and their interaction, it is a plethora of multiple metabolic defects that either cause or are associated or aggravate the hyperglycemic state.

Suggested Reading

1. Cersosimo E, Mandarino LJ, DeFronzo RA. Chapter 6 Pathogenesis of type 2 diabetes mellitus. [Online] Available from http://www.endotext.org/diabetes/diabetes6/diabetesframe6.html [Accessed September 2013].
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MANUAL OF
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Key Features

- Provides a focused up-to-date summary of diabetes and its management
- Relevant scientific information, integrated throughout with a focus on providing therapeutic guidance to the clinician
- Summarizes the available evidence on the use and efficacy of various drug-classes in the management of different forms of diabetes
- Written in an easy-to-read and image intensive format in order to simplify concepts
- Covers the complications of diabetes in detail
- Targeted towards diabetologists, physician, registrars, and post graduate students.

"I congratulate Dr Rajeev Chawla on compiling this state-of-the-art and up-to-date book on diabetes. It is very comprehensive and yet written in a simple style with excellent illustrations. As diabetes has become a huge problem in India I am sure it will be a huge success and I wish him all the best."

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