

Review Article

Pathophysiology & Management of Type 2 Diabetes: Past, Present and the Future

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Abstract

Diabetes is a metabolic disorder characterized by hyperglycemia resulting due to defects in insulin secretion, insulin action or both. Type 2 diabetes mellitus is the most common form of diabetes worldwide and its incidence is increasing exponentially due to lifestyle changes and increasing prevalence of obesity. Both genetic and environmental factors contribute to its development. Though insulin resistance and consequent beta cell dysfunction have been described as the two basic defects in the development of type 2 diabetes, recent research has thrown light on several other mechanisms including dysfunctional adipocytes, defective incretin action, mitochondrial injury, endoplasmic reticulum stress and defective gut brain axis. Modern management of type 2 diabetes includes lifestyle modification measures; oral anti-diabetic agents aimed at managing different patho physiological aspects of diabetes and insulin therapy in uncontrolled diabetes. Cardio vascular risk factors should also be aggressively treated.

Key Words : Type 2 diabetes, insulin resistance, adipocytes, incretin, free fatty acids

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Type 2 diabetes mellitus is associated with serious microvascular and macrovascular complications leading to higher morbidity and premature mortality. It was considered a condition of minor significance to world health a few decades ago but has become a major concern to public health especially in India with the number of people diagnosed with type 2 diabetes increasing dramatically in the last 25 years. India has the distinction to have the largest diabetic population, only next to China in the world. At present there are more than 2 crore individuals with diabetes in India and this is estimated to increase to 5.7 crores by 2025¹.

It is well known that type 2 diabetes is preceded by a long asymptomatic period where individuals deteriorate from normal glucose tolerance to impaired glucose tolerance and are later diagnosed with type 2 diabetes. This period approximates between 10 to 15 years differing in individual subjects. It is noted from epidemiological studies that impaired glucose tolerance

(IGT) and impaired fasting glycaemia (IFG) are metabolic states with increased risk of future type 2 diabetes, of which at-least 30-50 percent go on to develop diabetes^{2,3}. Recent data from the Diabetes prevention programme study in the US showed that these prediabetic states are also associated with increased incidence of microvascular complications⁴. There is now good evidence that lifestyle or pharmacological interventions at this stage are beneficial in preventing or delaying the onset of diabetes^{5,6}. In this review we discuss the pathogenic mechanisms responsible for the change from normal glucose tolerance to pre-diabetes and type 2 diabetes.

Type 2 Diabetes clusters in families and studies in first-degree relatives of type 2 diabetic parents and in twins have provided strong evidence for the genetic basis of insulin resistance and β -cell dysfunction. At least 40- 50 % of siblings of subjects with type 2 diabetes can expect to develop the condition. The risk

of developing diabetes was estimated at 2 to 4 times in offspring's with one or two affected parents. Further evidence comes from a number of twin studies, where monozygotic twins who share identical genetic information showed that the concordance rate for type 2 diabetes was significantly increased at 58% compared with the expected background population⁷⁻⁹. Prevalence of type 2 diabetes varies greatly between ethnic populations and in different parts of the world. It remains a common question whether this increased risk in certain populations is due to common environmental or genetic determinants. The genetic influence is supported by the fact that type 2 diabetes has a higher prevalence in certain populations like Asian Indians, American Indians and Pacific islanders. The prevalence is even higher when there is limited foreign genetic mixture as shown in Pima Indians⁸.

Thrifty genotype hypothesis

Neel et al postulated that humans are genetically programmed for the hunter-gatherer era and carry an evolutionary advantageous thrifty genotype which promotes increased lipid storage in times of plenty, which would then confer a survival advantage during famines and natural disasters¹⁰. This would explain the increased incidence of obesity and type 2 diabetes in Pima Indians, Australian Aborigines and Pacific

Islanders who until recently have followed a traditional lifestyle. When these populations are exposed to a Western diet with excessive energy through simple carbohydrates and increased saturated fat intake accompanied by a reduction in physical activity, the favourable metabolic profile becomes a handicap leading to obesity and type 2 diabetes¹⁰.

Thrifty phenotype hypothesis

Barker and Hales hypothesised that intrauterine malnutrition leads to low birth weight and permanent changes in structure and function in the foetus, which predispose these individuals to have a higher risk of diabetes in adult life. This has been postulated on the basis of epidemiological observations linking low birth weight to hypertension, obesity and diabetes. Due to the strong genetic nature of type 2 diabetes it could also be said that the surviving low birth weight babies are also an example of the thrifty genes¹¹. Type 2 diabetes is caused by a combination of impaired insulin action, defective insulin secretion and inadequate suppression of hepatic glucose output (figure 1). During a meal, the normal response is to suppress hepatic glucose output (HGO) and to enhance glucose uptake in the liver and muscle¹². This needs an appropriate insulin secretory response and adequate hepatic and muscle insulin sensitivity for glucose uptake. It is important to note that pre-diabetes forms a part of continuum between normal glucose tolerance and diabetes. And clearly most abnormalities like insulin resistance and defects in beta cell function which have been noted in the diabetic state have been identified in pre-diabetic individuals and even in glucose tolerant first degree relatives of subjects with type 2 diabetes. It is evident that these changes happen long before the development of diabetes¹³.

Does insulin resistance or beta cell dysfunction play an important role?

Insulin resistance is present in at least 90% of individuals with type 2 diabetes and equally in individuals with IGT. But not all individuals with insulin resistance develop type 2 diabetes. As long as the beta-cells are able to augment their secretion of insulin sufficiently to offset the insulin resistance, glucose tolerance remains normal. In individuals with preponderance to type 2 diabetes, there is a limitation to this hypersecretion of insulin. The onset of type 2 diabetes is associated with no further deterioration in insulin sensitivity; rather insulin secretion declined and fails to compensate for prevailing insulin resistance¹⁴. Data from newly diagnosed type 2 diabetic subjects in the UKPDS study clearly showed that subjects had already lost 50% of their beta cell function when a clinical diagnosis of diabetes is made¹⁵. Hence in pre-diabetes, with time the beta-cells begin to fail and initially the postprandial plasma glucose levels and subsequently the fasting plasma glucose concentration begins to rise, leading to the onset of overt diabetes.

Muscle

Skeletal muscle is responsible for 80% of glucose disposal in peripheral tissues and hence plays an important part in regulating carbohydrate metabolism. Glucose uptake in muscle is activated by the binding of insulin to its glycoprotein receptor which is located in the plasma membrane. This insulin receptor has two alpha and two beta units and binding of insulin to the alpha units leads to phosphorylation of specific tyrosine residues in the beta subunit thereby resulting in activation of the receptor. This leads to activation of various pathways inside the cell leading to stimulation of glycogen synthesis, protein synthesis, lipid synthesis, mitogenesis and activation of the GLUT4. In type 2 diabetes the ability of insulin to stimulate glucose uptake in muscle, glycogen synthesis and glucose oxidation are impaired¹⁶. These defects have also been identified in individuals with IGT and glucose tolerant first degree relatives of type 2 diabetes¹². In individuals with IGT as in type 2 diabetic individuals, the most proximal defect in the signalling pathway has been identified as the inability of insulin to stimulate tyrosine phosphorylation of its receptor. Defects in the activation of insulin receptor substrate-1 (IRS-1) and reduced ability to associate with the p85 subunit of phosphatidylinositol-3 (PI-3) kinase have been identified recently^{17,18}. Other studies have noted decreased activation of PI-3 kinase and reduced GLUT4 translocation. Work on human skeletal muscle cultures from insulin resistant normal glucose tolerant first degree relatives of type 2 diabetes identified a defect in insulin mediated glycogen synthesis¹⁹.

Liver

Type 2 diabetes is characterised by a raised fasting blood glucose which is associated with increased hepatic glucose production (HGP). In normal individuals, HGP is suppressed markedly even with small increments of insulin. In individuals with diabetes this sensitivity is lost in spite of hyperinsulinemia²⁰⁻²². Hepatic glucose production is also regulated by factors

such as glucagon and FFA which stimulate HGP. In vitro studies have demonstrated that plasma FFA are potent stimulators of HGP and do so by increasing the activity of pyruvate carboxylase and phosphoenol pyruvate carboxykinase, the rate limiting enzymes for gluconeogenesis^{23,24}. Reduced suppression of hepatic glucose production has also been found in subjects with IGT²⁰.

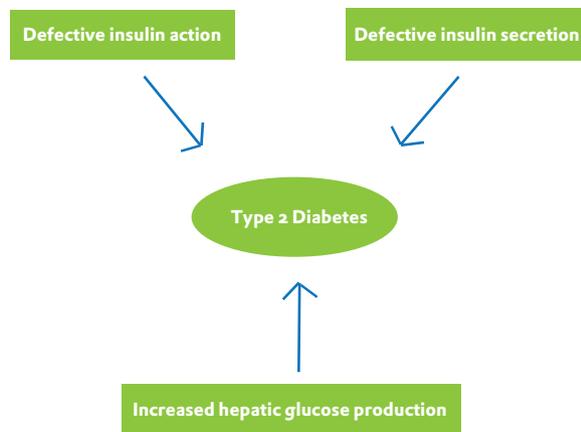


Fig1. Pathogenesis of Type 2 Diabetes

From the Triumvirate to the Ominous Octet

Recent evidence has accumulated to expand the conventional thinking of insulin resistance, reduced beta-cell function and increased hepatic glucose output as major factors for type 2 diabetes. New evidence in favour of the fat cell, incretin pathway, the alpha cells of islet of Langerhans, kidney and the brain as key regulators of glucose metabolism have become more evident in the last decade²⁵.

Fat Cell

Fat cells are resistant to insulin's antilipolytic effect, leading to day-long elevation in the plasma FFA concentration. Chronically increased plasma FFA levels stimulate gluconeogenesis, induce hepatic and muscle insulin resistance and impair insulin secretion. FFA also enhance the activity of glucose-6-phosphatase, the enzyme that ultimately controls the release of glucose by the liver²⁶. Dysfunctional adipocytes produce excess amount of pro-inflammatory adipocytokines like IL-6, TNF - α , Leptin and Visfatin which induce insulin resistance and atherosclerosis. Also, they fail to secrete normal amounts of insulin-sensitizing adipocytokines such as adiponectin. Enlarged fat cells are insulin resistant and have diminished capacity to store fat. When adipocyte storage capacity is exceeded, lipid "overflows" into muscle, liver, and β -cells, causing muscle and hepatic insulin resistance and impaired insulin secretion. Lipid can also overflow into arterial vascular smooth cells, leading to the acceleration of atherosclerosis²⁷.

Incretins

Gut-derived hormones (Incretins) are secreted in response to oral ingestion of nutrients that potentiate

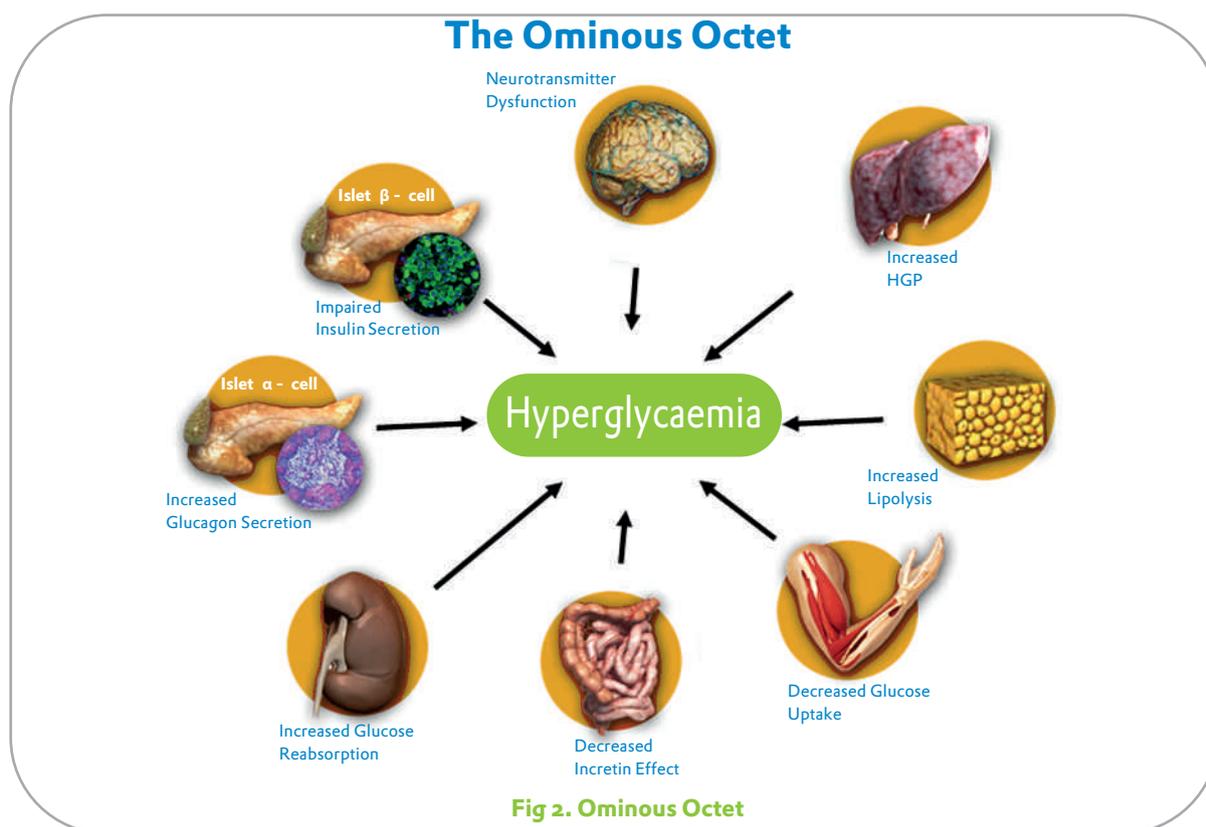
insulin secretion and suppress glucagon secretion in a glucose-dependent fashion. Two predominant incretins are Glucagon-like peptide-1 (GLP-1) and Glucose-dependent insulinotropic peptide (GIP). GLP-1 is rapidly inactivated by dipeptidyl peptidase-4. Upon food ingestion, GLP-1 is secreted into the circulation from L cells of small intestine. GLP-1 increases glucose-dependent insulin secretion, reduce the rate of gastric emptying and decrease postprandial glucagon secretion. GLP-1 has an indirect benefit on beta-cell workload, since decreased glucagon secretion will produce decreased postprandial hepatic glucose output. It has effects on the central nervous system, resulting in increased satiety and a reduction of total food intake^{28,29}. These actions, collectively called the "Incretin effect" is impaired in type 2 diabetes.

Glucagon

Glucagon secretion has been noted to be increased in type 2 diabetics and found to contribute to hyperglycemia mostly through glycogenolysis and gluconeogenesis. Increased glucagon levels in Type 2 diabetes leads to increased hepatic glucose output leading to elevated fasting blood glucose. Increased glucagon has been noted in postmenopausal women with IGT. Abnormal glucagon response in IGT is normalised by adequate insulinisation as in Type 1 diabetes. Glucose and insulin suppress glucagon secretion. Increased glucagon in the presence of the above proves inadequate suppression of alpha cell. Alpha cell insensitivity to insulin may be just a part of tissue insulin resistance leading to hyperglucagonemia. Alpha and beta cells may be regulated in parallel through autonomic nerves in the endocrine pancreas. Recent reports suggest an inverse relationship between plasma glucagon levels and insulin sensitivity. There is also evidence that the liver may be hypersensitive to the stimulatory effect of glucagon in hepatic gluconeogenesis³⁰.

Kidney

The most recent and unexpected member implicated in the pathogenesis of type 2 diabetes is the kidney. The kidney filters approximately around 162 grams of glucose every day. Ninety percent of the filtered glucose is reabsorbed by the high capacity SGLT2 transporter in the convoluted segment of the proximal tubule and the remaining 10% of the filtered glucose is reabsorbed by the SGLT1 transporter in the straight segment of the descending proximal tubule. The result is that no glucose appears in the urine. In animal models of both type 1 and type 2 diabetes, the maximal renal tubular reabsorptive capacity for glucose is increased. Thus, an adaptive response by the kidney to conserve glucose, which is essential to meet the energy demands of the body, especially the brain and other neural tissues, which have an obligate need for glucose, becomes maladaptive in the diabetic patient. Instead of dumping glucose in the urine to correct the hyperglycemia, the kidney chooses to hold on to the glucose. Even worse, the ability of the diabetic kidney to reabsorb glucose appears to be augmented by an absolute increase in the renal reabsorptive capacity for glucose. In summary, the development of medications



that inhibit renal proximal tubular glucose reabsorption provides a rational approach to the treatment of type 2 diabetes³¹.

Brain

Last but not the least an important player in the pathogenesis of type 2 diabetes is the brain. It is widely accepted that the current pandemic of type 2 diabetes is related to the ever expanding problem of obesity in all populations. It is suggested that the peripheral insulin resistance which is prevalent in pre-diabetes and obesity may extend to the brain. The most important areas for regulation of appetite are the ventromedial and paraventricular nucleus of the hypothalamus. The magnitude of the inhibitory response following glucose ingestion is reduced in obese, insulin-resistant, normal glucose tolerant subjects, and there is a delay in the time taken to reach the maximum inhibitory response. It is also suggested that this could lead to increased HGP and reduced glucose uptake in the muscle³².

Treatment of type 2 diabetes mellitus

Although several newer drugs targeting various patho-physiological aspects of type 2 diabetes mellitus are being introduced in the market, lifestyle intervention remains the cornerstone in the management of type 2 diabetes mellitus. The components of lifestyle intervention include medical nutrition therapy, exercise recommendations and comprehensive diabetes education. As majority of type 2 diabetics are obese, the goals of lifestyle intervention measures are:

- Achieving weight reduction- 5-7% of initial weight.

- Improving glycemic control.
- Improving insulin sensitivity.
- Cardiovascular fitness and
- Management of co-morbidities like dyslipidemia and hypertension.

Medical Nutrition Therapy (MNT)

Reduced calorie intake through reduction in carbohydrate (eg. avoiding sugar sweetened beverages) and fat intake (saturated fat <7% of total calories), carbohydrate counting and meal exchanges, optimal protein (0.8-1.0g/kg of body weight), dietary fiber (14gms/100kcal) intake, consumption of alcohol and non-nutritive sweeteners within the acceptable daily intake levels and individualized meal planning are the key components of MNT³³.

Physical activity

People with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals [4-6]. Diabetic patients with multiple cardiovascular risk factors should be screened for coronary artery disease before initiating exercise training program.

Pharmacotherapy

The major group of drugs used in the management of type 2 diabetes mellitus include:

1. Insulin Secretagogues- Sulphonylurea (Glibenclamide, Glipizide, Gliclazide, Glimeperide) & Meglitinides (Repaglinide & Nateglinide).
2. Insulin sensitizers- Metformin & Thiazolidinediones (Pioglitazone).
3. Incretin based therapies- GLP-1 Analogues (Exenatide and Liraglutide) & DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin and Linagliptin).
4. Alpha Glucosidase inhibitors- Acarbose, Voglibose & Miglitol.
5. Bromocriptine.
6. Insulins- Human insulins & Insulin analogues.

The guidelines for using these drugs are laid down and periodically revised by major international organizations like American Diabetes Association (ADA), European Association for the study of Diabetes (EASD) and American Association of Clinical Endocrinologists (AACE). The goals of therapy are to maintain optimal levels of fasting, post-prandial plasma glucose levels and HbA_{1c} (<6.5% as per AACE guidelines and <7% as per ADA guidelines). However, the choice of therapy should be individualized based on the age of the patient, duration of diabetes, presence of co-morbidities like obesity, nephropathy, coronary artery disease and most importantly risk of hypoglycaemia.

Metformin (unless contra-indicated or not tolerated) is the drug of choice for patients who have sub-optimal glycemic control after life style modification measures. As Metformin addresses the basic pathophysiology (Insulin resistance) of type 2 diabetes mellitus, helps to achieve glycemic control with negligible hypoglycemic risk, does not cause weight gain and reduces the cardiovascular risk in diabetics, it is still considered as the first choice even after several years of its

introduction. Sulphonylurea or Incretin based therapies are considered as second line drugs if glycemic targets are not achieved even after adhering to lifestyle measures and use of Metformin. Because of the risk of hypoglycemia and weight gain, Sulphonylureas are slowly being replaced by Incretin-mimetics as second line agents.

The role of Incretins in the pathophysiology of type 2 diabetes has already been discussed. Consequently, GLP-1 analogues (which delivers supra-physiological doses of GLP-1 when injected subcutaneously) and oral DPP-4 (An enzyme which degrades endogenous GLP-1) inhibitors have been developed for the management of type 2 diabetes. These drugs are either weight neutral (DPP-IV inhibitors) or produce weight loss (GLP-1 analogues).

Their use is associated with lesser incidence of hypoglycemia than Sulphonylureas. However, the cost of the therapy and the unknown long term side-effects limit their use in many Indian patients with type 2 diabetes. Although oral gliptins such as sitagliptin, saxagliptin and vildagliptin have now established as market leaders, there remains an array of newer gliptins such as linagliptin and dutogliptin which are due to make a mark in the Indian market. Despite the limited success of the more potent injectable counterparts such as exenatide and liraglutide, there are also newer versions such as albiglutide and Taspoglutide in the final phases of drug research. A long-acting version of exenatide is also available in Europe.

Rosiglitazone, a drug belonging to the group of Thiazolidinediones, was withdrawn from market due to increased cardiovascular risk. Another drug in this group, Pioglitazone is still being used in the management of type 2 diabetes, though it produces weight gain, edema, anaemia and increased risk of fractures. There is evidence that the incidence of malignancies of the urinary bladder could be increased after use of pioglitazone and hence has to be used cautiously. Other drugs like Alpha-glucosidase inhibitors and Bromocriptine are mainly used as add-on therapies due to their less significant effect on HbA_{1c}.

Properties	GLP-1 Analogues	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Insulin secretion	Enhanced	Enhanced
Glucagon secretion	Suppressed	Suppressed
HbA _{1c} reduction	-0.6% to -1.9%*	-0.5% to -0.8%*
Posprandial hyperglycemia	Reduced	Reduced
Body weight	Reduced	Neutral
Appetite	Suppressed	No effect
Gastric emptying	Delayed	No effect
Hypoglycemia	Low rate	Low rate
Gastro-intestinal effects	Nausea, Vomiting	No side effects
Cardiovascular risk factors	Decreases with weight loss	No consistent change

*-Average values obtained from several studies

Table 1. Comparison of GLP-1 analogues and DPP-4 inhibitors

Another class of agents which has shown promising results are the Sodium dependent glucose transport (SGLT₂) inhibitors. They block the reabsorption of glucose by the kidney thereby promoting glycosuria in consequence improving blood glucose levels in patients with type 2 DM. Although the theoretical possibility of urinary tract infection remains, the real risk seems to be negligible in large clinical studies. Dapagliflozin has been approved in Europe and Canagliflozin is currently being evaluated by the FDA. However, the US FDA has not approved Dapagliflozin due to a numerical increase in breast and bladder cancer seen in the clinical studies. Protein tyrosine phosphatase 1B (PTP1B) inhibitors, Adenosine monophosphate-activated protein kinase (AMPK) activators, Ghrelin receptor antagonists, Glucokinase activators are in phase 2 and 3 clinical studies and may be available as treatment for Type 2 Diabetes, Metabolic syndrome and Obesity.

Insulin therapy in type 2 diabetes is considered in situations like 1) failure to achieve target HbA_{1c} even after combination drug therapy – progression of Type 2 diabetes 2) Emergency situations like Diabetic ketoacidosis, Hyperosmolar Hyperglycemic states, acute illnesses, peri-operative period and pregnancy.

Progression of Type 2 diabetes due to the loss of pancreatic beta-cell function irrespective of glycaemic control remains a significant disadvantage of conventional diabetic therapies. Established drugs for treating type 2 diabetes i.e. insulin, sulfonylureas, and glitazones also cause weight gain. Severe hypoglycaemia remains a serious risk with improving glycaemic control, especially with insulin and the sulfonylureas. There remains a need to develop new anti-diabetic drugs that lower blood glucose, while promoting weight loss and slow the progression of the disease. In the long-term; glucose lowering drugs should also have favourable effects on morbidity and mortality from microvascular and macrovascular complications of diabetes.

Summary

The pathophysiology of type 2 diabetes mellitus had been a subject of extensive research in the past decade. As a result, newer mechanisms were included to form an "Ominous octet" instead of the old "Triumvirate". Consequently, these newer targets provide scope for expansion of the therapeutic armamentarium of type 2 diabetes. Present and future research should be more focussed on the concept of "beta cell regeneration" and hence prevent progression of type 2 diabetes. This will be a major breakthrough in the management of type 2 diabetes and hopefully arrest the current diabetes pandemic.

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