Advances in diagnosis and treatment of Diabetes Mellitus

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Abstract
Diabetes is a highly debilitating disorder with far reaching medical consequences. The development of detection and diagnostic techniques for this disorder is outlined and novel strategies to combat it based on its biochemistry are discussed.

Introduction
The World Health Organization estimates that today over 180 million people have diabetes and this figure is likely to double in the next two decades. In 2005 alone 1.1 million people died as a result of diabetes and 80% of these deaths were in low and middle income countries. It is reported that if further action is not taken the number of deaths due to diabetes and related disorders could go up by 50%. Diabetes is thus, one of the deadliest disorders and is also a huge economic burden in terms of health care costs. The United Nations, on 20th December 2006 signed a resolution against making it the first not infectious disease to be recognized as a chronic, debilitating and costly disease. Thus the potential of this disease to pose as a sever risk to individuals, families and even entire nations is now recognized and it is imperative that appropriate measures are taken to deal with it.

While the current techniques to combat this disorder do allow patients to live longer and better lives, they are not very efficient and new strategies need to be developed prevent or cure this disorder. Towards this end, a lot of work is being done to understand the molecular and genetic basis of this disease. Research such as this would help develop novel strategies that not only aim to cure the symptoms of the disease but also target its root causes.

This report discusses some of the recent advancements in diabetes research and outlines some new strategies to combat this disorder. It begins with a brief description of the disorder and its effects, followed by an account of how diabetes treatment techniques have developed over time. It then goes on to discuss the molecular and genetic basis of the disease and some diagnostic techniques and drugs based on these. A brief account of certain herbal remedies
is also presented. Finally some novel anti diabetic strategies are outlined.

Types of Diabetes
Traditionally, two forms of diabetes were known, diabetes insipidus and diabetes mellitus. Of these diabetes mellitus, is the lethal one is the focus of this report. Diabetes mellitus, now referred to simply as diabetes, is further classified as by the WHO on the basis of clinical observations and treatment requirements as insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM). IDDM is also known as childhood-onset diabetes or DM1, while NIDDM is referred to as adult-onset diabetes mellitus or T2DM. Another form of diabetes is gestational diabetes mellitus (GSM) that occurs due to an increased in the amounts of insulin antagonistic hormones like estrogen, progesterone, human chorionic gonadotropin, somatomammotrophin and corticosteroids during pregnancy and is generally temporary.

The root cause of DM1 is the autoimmune destruction of pancreatic islets of Langerhans. The islet cells are a major site for insulin production and their destruction leads to drastic fall in the insulin levels causing hyperglycemia. People who lack protective alleles of the human leukocyte antigen (HLA) or major histocompatibility complex are most susceptible to this disorder and since these genetic defects manifest early DM1 is generally found in adolescents.

T2DM on the other hand is caused due to insensitivity peripheral tissues like muscles, livers and adipose to insulin. This condition is generally diagnosis in adults and is more prevalent among some races. 90% of people diagnosed with diabetes fall under this category. Although the cause of DM2 is not clear, several factors are believed to be responsible. These include certain genetic traits that promote insulin resistance, obesity, lack of proper exercise etc.

Hence effective diabetes treatment involves alterations in diet and lifestyle along with the use of oral drugs and insulin. These simple measures allow diabetics to live healthier and longer lives than was thought possible a century ago.

History of diabetes detection and treatment
The earliest discovered written record of the symptoms of diabetes was found on a 3500 year old scrap of Egyptian papyrus[37] that noted symptoms such as frequent drinking of water, excessive urination and sweetness of the urine. Owing to these symptoms, diabetes was thought to be a disorder of the kidneys and bladder up
until the 19th century.

Though many researchers validated these symptoms it wasn't until 1889 that the pancreas was first suggested as the origin of this disorder. At the time Oskar Minkowski was investigating the role of the pancreas when he noticed diabetes-like symptoms in a dog whose pancreas had been surgically removed\(^\text{[29]}\). After investigating this further, Minkowski and his colleague Joseph von Mering concluded that the pancreas secreted a substance that affected the body's metabolism of sugar and an imbalance in the secretion of this substance led to diabetes. These initial discoveries led to a flurry of research to study the connection between diabetes and the pancreas and several efforts were made to isolate the substance hypothesized by Minkowski.

One such researcher, who was very interested in diabetes and its cause, was a Canadian doctor, Frederick Banting. By the 1920s, it was known that a protein hormone was secreted by the islets of Langerhans\(^\text{[23]}\) in the pancreas and this hormone, named Insulin by Schaffer\(^\text{[43]}\), was responsible for the metabolism of sugar. And hence a deficiency of insulin led to the accumulation of sugar in the blood. However, all efforts to isolate insulin from the pancreatic extracts had failed and hence the specific effects of this hormone could not be studied. This was attributed to the fact that the insulin in pancreatic extracts was broken down by other pancreatic enzymes making it impossible to isolate. However, it was also known that blocking the pancreatic duct, killed only the enzyme producing cells, the acini in the pancreas, while the islets of Langerhans remained intact. With this in mind, Banting proposed in 1921 that if he first killed the acini he would be able to isolate insulin. This proved to be one of the major breakthroughs in the treatment of diabetes. And Banting, together with Charles Best, successfully isolated a portion of the pancreatic extract that immediately lowered the blood sugar level in severely diabetic experimental animals. The ability of this extract to alleviate the symptoms of diabetes was further demonstrated when it was used to restore a 14 year old skinny almost skeletal, diabetic boy back to good health within a few months. For his remarkable work Banting was awarded the Nobel Prize in Physiology and Medicine in 1923.

The next major step in understanding and diagnosing this disorder came in 1930 in the form of a study published by Harry Himsworth\(^\text{[16]}\). Based on his experiments, Himsworth concluded that there were two related forms of diabetes. One was caused by the body's inability to make insulin and the other by the body's insensitivity to it. These disorders were named type 1 diabetes and type
2 diabetes respectively. Himsworth also noted that type 1 diabetes was caused by the pancreas' inability to secrete insulin and this usually developed at a young age. On the other hand, type 2 diabetes was a result of the body's insensitivity to insulin and was commonly found to occur at an older age. These claims were later validated by Rosalyn Yalow and Solomon Berson, who in doing so also invented the radioimmunoassay technique for which Yalow received a Nobel Prize in 1977.\[5\] Thus, by the late 19th century, diabetes had been pretty well understood and researchers realized that it was a long term disorder that began several years before its symptoms became obvious. Many researchers even recognized a pre-diabetic condition that was found to exist before the onset of diabetes and gave it the name “metabolic syndrome”. The symptoms of this syndrome include high blood levels of triglycerides, low levels of high density lipoproteins and high blood pressure. Other disorders attributed to diabetes were obesity and an elevated risk of a heart attack.

In parallel to understanding the molecular basis of diabetes, researchers in the 19th century were also striving to develop oral drugs that would supplement insulin in diabetes treatment. One of the first of these drugs was discovered by Marcel Janbon of the French University during the Second World War. This drug was sulfonylurea, and it stimulated the pancreas to release insulin. In 1958 the first sulfonylurea based anti diabetic drug hit the markets and it typically delayed the need for insulin in patients by several years. Soon other drugs were discovered that were also effective in controlling diabetes. Prominent among which was metformin that was commercially marketed in the 1960s under the name of Glucophage. Apart from controlling diabetes by regulating insulin production and promoting muscle uptake of glucose, it also decreased triglyceride levels and thus reduced risks of heart attacks.

As the understanding of the disease grew, more and more potential strategies to combat it were developed. Now there are several anti diabetic drugs on the market that act in a variety of ways and target in conjunction with insulin treatment or on their own allow diabetic patients to live normal, healthy lives.

The genetic and molecular basis of diabetes
A review of the many complications induced by diabetes, and its prevalence in different demographics suggests that type 2 diabetes mellitus is essentially a lifestyle disorder. Its prevalence is greater among the more modernized nations where the lifestyle is mainly sedentary and energy rich processed food is in plenty. According to this line of
thought, many risk factors for diabetes mellitus have been identified such as old age, specific nutritional factors, obesity, physical inactivity and stress all of which are fall outs of a modern lifestyle.\cite{56} The WHO has also defined the pre-diabetic state, the metabolic syndrome as the simultaneous occurrence of any two disorders out of hypertension, dyslipidaemia, obesity or microalbuminuria in an individual. Individuals with such a condition are at a greater risk of diabetes.\cite{14} Factors such as plasma leptin, tumor necrosis factor-α and non-esterified fatty acid levels are all elevated in obese people and these play a role in causing insulin resistance.\cite{24}

The thrifty gene theory was proposed to account for relation between a modernized life style and diabetes. This states that, among early humans the genes selected for were the ones that fostered deposition of fat and storage of calories in times of plenty and provided a selective advantage during the time of famine. However with the shift to the current modernized life style, where famines are rare and lifestyle is sedentary, this selective advantage is lost. As a further proof to this theory, it is observed that the incidence of diabetes is highest amongst the Pima Indians, whose populations were most subjected to adverse conditions and consequently would have the highest probability of harboring the thrifty genotype.\cite{17}

It has also been reported that variants of genes such as those responsible for glucose uptake in skeletal muscles and regulation of lipolysis among others, could be a large part of the set of thrifty genes.\cite{14} A mutation of the gene coding for the enzyme glucokinase present on chromosome 7p is known to delay the insulin response to glucose levels. Other specific genetic traits that have been associated with T2DM are mutants of the gene HNF4α on the chromosome 20q and HNF1α on chromosome 12q both of which gives rise to hepatic insensitivity of insulin. Certain mitochondrial gene mutations are also known to be associated with diabetes mellitus.

While many different molecular factors have been implicated to varying degrees in the development of diabetes mellitus, most of them are all connected in some way to the insulin signal transduction pathway. Upon binding to the insulin receptor, insulin activates a series of signal transduction events that result in specific biological actions. This biochemical cascade starts with autophosphorylation of the insulin receptor and the subsequent phosphorylation of insulin receptor substrates (IRS). This phosphorylation of IRS leads to the activation of the phosphatidylinositol 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways. Stimulation of glucose transport and disposal, glycogen synthesis, and
inhibition of lipolysis are mediated by PI3K activity, whereas MAPK promotes cell growth\cite{41}. In most cases insulin resistance develops as a direct result of the impaired activation of this signaling cascade, resulting in inappropriate glucose and lipid metabolism.

**Diagnosis of diabetes**

Since diabetes leads to a plethora of imbalances in the body, many different factors can potentially be used as markers for diagnosis. However, the most commonly used factors screened for, are glucose and glycohemoglobin\cite{46}. Off late portable hand held, amperometric sensors that monitor blood glucose levels have become common place. These sensors, first developed in the 1980s, rely on the oxidation of glucose by glucose oxidize. Other diagnostic tests include measuring the serum levels of glycated hemoglobin such as HbA1c, which are adjuncts formed between glucose and hemoglobin in the blood and are a good indication of the progression of diabetes. These glycohemoglobins are detected by techniques such as ion exchange chromatography, affinity chromatography and immunoassays. More recently, artificial sensors with high binding affinity to saccharides have been developed that efficiently and accurately detect glucose levels in the plasma. Also common place now is the oral plasma glucose tolerance test or the fasting plasma glucose tests, that require a patient to fast for eight to twelve hours before drinking a glucose containing solution and then measure blood glucose levels. Glucose concentrations higher than 140 mg/dl or 200 mg/dl are indicative of pre-diabetes (impaired glucose tolerance) or diabetes respectively.

Another marked effect of hyperglycemia is the cell damage induced by metabolic imbalances. Hyperglycemia typically increases oxidative stress on cells, causing peroxidation of lipids and oxidation and formation of carbonyl groups in proteins. These groups can in turn be used as markers by monitoring their reaction with antioxidants like superoxide dismutase (SOD) and glutathione peroxidase (Gpx) and catalase\cite{39}. A more direct approach, reported by Shuichi Otabe et al is measuring the C-peptide concentration in the plasma. C peptide is formed when proinsulin is cleaved to form insulin. In a related study the same group also identified a mutation in the transcription factor of the hepato-nuclear factor-α gene that is known to cause incidences of diabetes among children\cite{41}.

Another interesting indirect technique to detect elevated blood glucose levels is monitoring the increased concentration of acetone in exhaled air\cite{40}. It has also been suggested that low birth
weight could be an early indication of susceptibility to diabetes, due to impaired development of pancreas and other tissues\textsuperscript{[8]}. Another diagnostic trait for diabetes was reported by Tien Yin Wong et al who observed micro vascular blockages in retinal vessels among diabetic patients\textsuperscript{[49]}.

**Oral anti-diabetic drugs\textsuperscript{[8]}**

Traditionally anti diabetic drugs were developed to combat the obvious symptom of diabetes, the high blood glucose levels. Towards this end, several families of drugs have been developed most common amongst which are sulfonylureas, biguanide, thiazolidinediones and α-glycosidase inhibitors. It has also been shown that preemptive use of some of these insulin sensitizing drugs may help preserve endogenous insulin production and delay β-cell failure\textsuperscript{[22]}.

**Sulfonylurea:** This family comprises of some of the earliest discovered anti diabetic drugs, and even today they are the most widely prescribed. The common members of this family of drugs are carbutamide, tobutamide, chlorpropamide, acetohexamide and tolazamide. All of them stimulate the β-cells of the pancreas to produce insulin. Their active component, a -SO2-NH-CO-NH- group, leads to the opening of the calcium ion channel causing an influx of Ca\textsuperscript{+} ions and depolarizing the β-cells. This depolarization, due to further reaction cascades eventually result in the production of insulin. Sulphonylureas also delay the polarization of the β-cells by clocking K\textsuperscript{+} ion channels, thus sustaining insulin production for a longer time. Recently, however there is some evidence to show that in some cases, Sulphonylurea alone doesn't affect blood glucose levels and parallel insulin treatment is also required\textsuperscript{[18]}.

**Biguanide:** This is a family of guanidine derived drugs that include metformin, buformin and phenformin. Of these Metformin is the most popular and is generally administered to obese people. It works by decreasing the hepatic glucose production and enhancing insulin action in the peripheral tissues. Metformin increases the adenosine mono phosphate-activated protein kinase activity in hepatic cells and skeletal muscle cells, which in turn enhances insulin receptor kinase activity by increasing the activity of its gene GLUT-4\textsuperscript{[25]}. While metformin is now the most prescribed anti diabetic drug, recent research has shown that some patients do not respond to it alone and in these cases it metformin doses need to be supplemented with sulphonylureas\textsuperscript{[28]}. 
α-glycosidase inhibitors: This family of drugs, the most popular of which is acarbose, slow down the absorption of sugars in the intestines and thus reduce blood glucose levels. They are essentially saccharides that competitively bind to glucose digesting enzymes in the intestines. Acarbose for example interferes with the pancreatic α-amylase hydrolyses that break down starch to maltose, thus causing a postprandial fall in the glucose levels. These drugs also tend to increase insulin sensitivity by a mechanism that is not yet understood. Other drugs in this family include miglitol and voglibose. There is some evidence to show that Voglibose also has beneficial cardiac effects[26].

Thiazolidinediones: These drugs include rosiglitazone, pioglitazone, troglitazone and ciglitazone all of which bind to the PPARγ receptor molecules, ultimately leading to an increase in insulin production.

Apart from the above, some other drugs are also important in controlling diabetes. Among these are repaglinide, nateglinide also have the same mode of action as sulfonylureas. Repaglinide has also been shown to synchronize insulin secretion with meal digestion in order to reduce post-prandial hyperglycemia[36]. Other drugs such as the intestinal lipase inhibitor orlistat and the satiety-inducer sibutramine are weight-reducing agents that benefit glycaemic control in obese type 2 diabetes patients[36].

Herbal Remedies
Herbal anti diabetic remedies have existed long before the more modern oral drugs were discovered. Now a lot of work is being done to investigate the therapeutic properties of these medicinal plants with the aim of developing new anti diabetic drugs. The ethyl acetate extracts of Hemionitis arifolia, for example were shown to have marked ant diabetic properties in mice and were also devoid of toxic side effects. Further analysis attributed these therapeutic properties to certain steroids and coumarins and this finding has opened a whole new avenue for the development of anti-diabetic drugs[3]. A similar study has pointed pronounced anti diabetic properties in the methanol extracts of Barleria lupulina Lindl[45]. It has also been reported that feeding diabetic mice with Momordica charantia, Eugenia jambolana, Mucuna pruriens and Tinospora cordifolia extracts not only reduced their blood glucose levels but also slowed down diabetes associated renal damage[15]. Research by Saravanan et al. revealed that Cogent db, a common Indian herbal concoction is extremely efficient in decreasing blood glucose as well as serum and tissue lipids levels and in increasing
the amount of insulin and hepatic lipogenic enzymes [42].

Lia et al. have, on the other hand, investigated an alternate natural, anti diabetic strategy. They have reported the use of naturally occurring insulin analogs such as 1,2,3,4,6-penta-O-galloyl-d-glucopyranose, which can bind to insulin receptors and trigger the insulin-mediated glucose transport signaling pathway [28]. These and other such herbal remedies are hence a rich source of new, safe and effective anti diabetic medicines. Investigating the mechanisms by which these compounds combat diabetes will also help further our understanding of the disorder and its causes.

**Novel anti diabetic strategies**

In the past few decades a large amount of work has been done in trying to understand diabetes and its many effects on the body. As a culmination of these efforts we now have several novel strategies that hold great potential in preventing or curing this disorder [33].

A bulk of these strategies focus on directly or indirectly enhancing insulin production, and the class of molecules that bring about this effect are called insulin secretagogues. For example, it was discovered that obese people have large amounts of protein tyrosine phosphate (ptp), and this enzyme in large concentrations tends to dephosphorylase insulin receptors thus hampering the insulin signaling pathway. Consequently B.A. Zinker et al. and other demonstrated the use of ptp inhibitors in improving the insulin sensitivity of diabetic mice [11][57].

Similarly various other molecules that either positively or negatively regulate the insulin signal transduction pathway are being considered as targets for new therapeutic strategies. One such molecule is the SH2-domain-containing inositol 5-phosphatase (SHIP2) that negatively modulates the insulin signaling pathway by altering the activity of downstream targets like phosphatidylinositol-3-phosphates [32] suggesting that decreasing SHIP2 activity can be used to deal with hyperglycemia. Another similar molecule being considered is IκB kinase β (IKKβ) that activates the transcription factor NF-κB, since there is some evidence to suggest that this enzyme negatively regulates the insulin signaling cascade [53].

Other interesting strategies focus on regulating the hepatic glucose production. Towards this end Desai et al. have reported that up regulating the production of glycolytic enzymes such as glucokinase (GCK), which is the first enzyme in the glycolysis pathway, reduced the diabetes symptoms in mice [9]. A related study revealed
that up regulating 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, the enzyme that catalyzes the production and degradation of fructose-2,6-bisphosphate, leads to an increase GCK levels and can thus be used to control hyperglycemia\textsuperscript{[50]}. An alternate approach to reduce hepatic glucose production is to suppress glycogenolysis by inhibition of glycogen phosphorylase. This enzyme catalyzes the conversion of glycogen to glucose-1-phosphate (G-1-P) monomers, which are further metabolized to glucose. Inhibition of glycogen phosphorylase by the compound CP-91149 has shown favorable results in diabetic mice without producing hypoglycemia \textsuperscript{[41]}. Another anti hyperglycemic agent S-15261 has been shown to reduce hepatic glucose production by direct and insulin sensitizing effects on genes encoding regulatory the proteins of hepatic glucose metabolism \textsuperscript{[30]}. Circulating free fatty acids (FFAs) have also been known to induce insulin resistance in the liver and peripheral tissues when in elevated levels. They also impair glucose oxidation and promote hepatic glucose production. As a result a few strategies to prevent diabetes by inhibiting the accumulation of fatty acids are being proposed. Towards this end, an adipokine called adiponectin may serve useful. In skeletal muscles, adiponectin is known to up regulate genes that play an important role in lipid uptake and metabolism. It has also been reported that adiponectin mRNA levels are very low in diabetic patients \textsuperscript{[20][21]}. Furthermore it has been suggested that the TZD, rosiglitazone, decreases blood glucose levels by up regulating the adiponectin gene \textsuperscript{[52]}. It has also been reported that adiponectin reduced insulin resistance in diabetic mice by decreasing the triglyceride content in liver and muscle. Adiponectin is also known to enhance insulin action and reduce glucose output in isolated hepatocytes\textsuperscript{[4]}. The adipocytes also secrete a peptide hormone resistin, that is found in elevated levels in mice. It has also been demonstrated that administering resistin to mice reduces insulin tolerance. Hence strategies to reduce resistin activity, such as neutralizing it with antibodies are being considered as potential anti diabetic strategies\textsuperscript{[44]}. Another strategy targets AMP-activated protein kinase (AMPK). AMPK senses ATP availability of the cells and is activated when ATP levels deplete. The AMPK system is involved in turning on catabolic pathways and shutting down ATP consuming processes. The eventual result of AMPK activation in the liver is an increase in fatty acid oxidation and reduction in lipogenesis\textsuperscript{[34][13]}. It also promotes muscle cells to take up glucose by promoting the activity of the glucose transporter GLUT4. Some of the benefits of modern exercise are
also associated with its stimulation of the AMPK system. Thus it is hypothesized that a sedentary life style could impair AMPK activity and thus promoting the onset of diabetes mellitus\[47\]. Thus, up regulation of AMPK is being considered as a potential strategy against diabetes. G. Zhou et al have suggested that AMPK is involved in the inhibitory effect of metformin on glucose production in the liver and the stimulatory effect on glucose uptake by skeletal muscle\[54\]. R. Lupia et al have also suggested oxidative stress as a possible cause of β-cell damage in type 2 diabetes. They demonstrated that in human pancreatic islets form diabetic patients the use of an anti oxidant bis(1-hydroxy-2,2,6,6-tetramethyl-4-piperidinyl) decandioate di-hydrochloride reduced oxygen stress and normalized glucose induced insulin secretion\[30\].

The incretin system is also the focus of several anti diabetic strategies. Holst et al have concentrated on the incretin effect of the hormones Glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)\[19\]. It is known that GLP-1 enhances glucose-stimulated insulin secretion, regulates nutrient intake by inhibiting gastric emptying and enhancing satiety, and suppresses glucagon release\[10\]. GLP-1, has been reported to promote islet proliferation and neogenesis\[55\]. They found that in diabetics GLP1 secretion is reduced and GIP loses its insulinotropic effects. And administering GLP1 led to improved glucose profiles, decreased HbA1c levels and improved β-cell activity. Though very effective, one practical problem with this approach is that GLP-1 is degraded rapidly by dipeptidyl peptidase IV (DPP IV) in the gut. Thus researchers are now developing resistant GLP1 analogs and DPPIV inhibitors to make new drugs. For example Burcelin et al.\[6\] have developed encapsulated genetically engineered cells that secrete a modified version of GLP-1 with a longer half-life than naturally occurring one. When implanted into diabetic mice, GLP-1 production was achieved for several weeks, demonstrating this as a feasible approach to the long-term production of the peptide. DPP IV inhibitors like DP IV P32/98 and NVP DPP728 have shown good results\[38\] \[2\]. An alternate approach involves the use of NN2211, which is a GLP-1 derivative that is resistant to DP IV digestion and has shown anti-diabetic effects in Diabetes mellitus patients\[27\].

**Diabetes Treatment**

While we are still short of developing a complete cure for diabetes, proper care and treatment can go long way in delaying the disease or allaying its symptoms. The basic measures to control the progression of this
Disease are all aimed at regulating the plasma glucose levels. A proper diet and moderate amount of exercise are the most effective among these.

**Diet:** In recent years, it has been observed that good glycaemic control can be achieved by a regulated diet. A proper diet can go a long way in reducing excess body weight, improving glucose level control and serum lipid profiles. In general, diabetic patients should consume 2,000-2,500 calories/day to maintain an ideal body mass index [35]. Carbohydrates and monosaturated fat should provide approximately 60–70% of energy intake. Carbohydrates from whole grains, fruits, vegetables, and low-fat milk should be included in the diet. The average amount of carbohydrates recommended for patients is 40 to 60% of dietary intake.

It is known that soluble viscous fibers can reduce serum cholesterol levels, whereas fructose adds low-density lipoprotein cholesterol to the system. Wheat bran is also shown to improve glucose tolerances. There is no clear physiological evidence for this phenomenon, but believed that magnesium content may cause the carbohydrate tolerance.

The frequency of food intake and content of subsequent meals are also important factors in achieving proper glycaemic control. For example, a carbohydrate loaded by the first meal may facilitate the disposal of carbohydrates in the next meal, this is known as the Staub-Traugott effect [1]. Also, prolonged suppression of free fatty acids (FFA) levels shows an improved second meal glucose tolerance. Experiments show that FFA concentration from the first meal has an impact on the postprandial glycemia [48]. In the same context, better glycemic control is seen by nibbling rather than gorging.

**Exercise:** Exercise plays an important therapeutic role against diabetes. Exercise lowers blood glucose levels and transiently increases glucose tolerance. During fasting, the physiological blood concentrations of glucose are maintained by the liver. In the postprandial state, the rise in blood glucose concentration stimulates insulin secretion, which reduces hepatic glucose production and increases membrane glucose transporters (GLUT) in peripheral tissues, thus reducing blood glucose.

During exercise skeletal muscles require more energy for contraction, using blood glucose, muscle glycogen, and fatty acids as fuel. Exercise has been shown to result in decrease in the serum levels of triglyceride (TG), very low density lipoprotein (VLDL) cholesterol and an increase in high density lipoprotein cholesterol[31]. Other benefits include an
increase in the skeletal muscle mass, enhanced blood flow to the muscle and a greater density of insulin receptors, thus leading to better disposal of glucose.

Exercise programs for diabetic patients consist of aerobic exercises which enhance muscle mass and modify body composition. The duration of exercise is proportionally related to the caloric expenditure required (directly) and related to the intensity (inversely). 30 minutes of moderate and continuous exercise per session is recommended \[^{35}\]. To improve cardiovascular performance, the recommended frequency of exercise is between three and five sessions per week. Resistance training should be performed at low intensity, to avoid high blood pressure, with 10–15 repetitions for each muscle group and a 3:1 ratio of endurance/resistance sessions. There are several safe forms of exercise such as walking, jogging, bicycling, and swimming, which allow patients to maximize their caloric expenditure and to improve physical fitness enjoyably and effectively.

**β cell transplantation:** Apart from proper diet and exercise, another effective treatment is the use of Islet cell implants and pancreatic implants to deal with β cell impotency. The transplantation procedure is safe and relatively quick. A study showed that more than 50% of the people treated with implants showed insulin independence after 1 year \[^{12}\].

**Conclusion**

Diabetes mellitus has been recognized as an extremely deadly disorder with serious medical and economic consequences. Hence a lot of work is being done worldwide to develop cost effective sustainable ways to prevent or cure this disorder. Already several biochemical and genetic marker tests have been developed to screen for individuals who are most likely to develop diabetes. Proper care and some oral medication can delay it’s onset among these susceptible individuals considerably. While a complete cure is still illusive, research into the genetic and molecular basis of the disease has helped develop smart strategies that could one day cure this disorder completely.

**References**


