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New Frontier in the Treatment of Diabetes

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ABSTRACT

Diabetes mellitus is a group of metabolic diseases recognized by chronic hyperglycemia resulting from defects in secretion in insulin, insulin action or both. There are different types of diabetes like Type 1, type 2, gestational diabetes, secondary diabetes, wolfram syndrome and autoimmune polyglandular syndrome. Type 1 and type 2 diabetes are most common type of diabetes. Polydipsia, polyuria, polyphagia, weight loss slow wound healing, etc. are common symptoms of Diabetes. Diabetes can be genetic; autoimmune, medical related or even diet related. In this article causes and treatment of diabetes is discussed in detail. It includes glimpse of novel technologies like patches, pump and pens, etc. It also includes momentary of other treatment like oral and Injectable hypoglycemic drug and surgical treatments. A glance of latest innovation for measuring glucose level in body with help of sweat, breath and saliva are explained.

Keywords: Diabetes; Type 2 Diabetes Mellitus (TY2DM), Polydipsia, polyuria, polyphagia, clicksoft microinjection, insulin pen, v-go

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Introduction

Diabetes mellitus is a group of metabolic diseases recognized by chronic hyperglycemia resulting from defects in secretion in insulin, insulin action or both [1]. .Around 1500 B.C.E. ancient Egyptians were first to recognized Diabetes, it was considered a rare condition in which a person urinated excessively and lost weight.Earlier before 200 years diabetes was not documented and nothing was known about mechanism of action. No effective treatment was available and it was fatal within weeks to months after its diagnosis owning to insulin deficiency.[2] In 200 years, major approaches have been done in understanding of the underlying causes of diabetes and the approach to its prevention and treatment[2]. Diabetes is associated with reduction in life expectancy but outlook of disease has changed and patients lead active and productive life's for many years after diagnosis. Now a daysmany therapies are available for treating hyperglycemia and its complications but pathway to its cure has remained elusive. Since 1923, 10 scientists have won Nobel Prize for diabetes related investigations[2].

Causes of diabetes [3]

Main causes of diabetes are complex and cases with one of the two processes;

1. **Due to metabolism: -** Body ability to use insulin can be impaired due to lifestyle factors like overeating, physical inactivity and obesity. This is called insulin resistance. Genetics, family history and age can be included in uncontrollable risk factors.

Metabolic form of diabetes includes **A. Type 2 diabetes and B. Gestational diabetes**

2. Autoimmune: -Insulin-producing beta cells of the pancreas can destroyed mistakenly by body immune system. Causes of autoimmune diabetes are poorly understood but family history and genetics play a role. It includes A. Type 1 Diabetes

Diabetes is considered as a multi-factorial, involving risk factors and predisposing conditions. In many cases environment or genetics may contribute to aperson's diabetes. Autoimmune diabetes is more common in white people but type 2 and gestational diabetes is common among other ethnicities.

Prediabetes, insulin resistance and metabolic syndrome are strong risk factors. Major causes of diabetes are:-

1. Genetics and family history: - Maturity-onset diabetes of young (MODY) and Wolfram syndrome can be caused by certain genes.

2. Weight and Body type: - Obesity and overweight are leading factors in type 2 diabetes, Excess fat around the abdomen enhances the insulin resistance and metabolic syndrome.

Sufferers of type 1 diabetes are of normal weight but recent research indicates the development of type 1 diabetes due to obesity.

3. Level of physical activity: - Epidemics of obesity and diabetes is blamed due to lack on regular exercise.

4. Diet: - Development of diabetes due to the impact of diet is controversial. Studies show that heavy consumption of soft drink and other simple carbohydrates to risk of metabolic diabetes. Foods which have low glycemic index to reduced risk.

5. Other diseases: - High blood pressure, hyperlipidemia, polycystic ovarian syndrome, asthma and sleep apnea like medical conditions have been linked to type 2 diabetes. Type 1 diabetes have been linked to celiac disease (gluten intolerance) and other diseases. Many diseases may cause secondary diabetes include pancreatitis, hemochromatosis, Cushing's disease and acromegaly, Down syndrome etc.

6. Medical Treatment: - Secondary diabetes may result due to hormonal therapies, icatio like diuretics, beta blockers, immunosuppressive etc. Drugs like pentamidine(for pneumonia) and L-asparaginase have been connected with type 1 diabetes.

7. Smoking: - Cigarette smoking is factor for type 2 diabetes.

8. Alcohol :- It is risk factor for diabetes

Types of Diabetes.[3]

Various type of diabetes are known to man and some it are mentioned below:-

1. Type 1 diabetes: - In the insulin making beta cells of pancreases are mistakenly destroyed by our body our immune mistake. This an auto immune diseases. Its development is quicker than any other from of diabetes. Children, adolescent and young adult are usually diagnosed. Insulin must be administer regularly to survive.

Type 1 diabetes used to be called juvenile diabetes and insulin-dependent diabetes mellitus (IDDM). These are not accurate because other form of diabetes can be developed by children and adults can develop type 1 diabetes and insulin therapy is required for other forms of diabetes.

Latent autoimmune diabetes of adulthood (LADA) is variation of type 1 diabetes after usually occurs later in life after 30 years.

2. Type 2 diabetes: -Metabolic disorder involving insulin resistance and excess weight. In this type of diabetes insulin is initially produced by pancreases but body has trouble using this glucose controlling hormone. Ultimately enough insulin is produced to respond to body requirements. According to the international Diabetes Federation, type 2 diabetes accounts for 85% to 90% in developed nation and more number of cases in developing nation. Type 2 diabetes is most common form of diabetes.

Development of diabetes may take decades or years. It is usually preceded by prediabetes, in which blood sugar is above normal but not high enough for diagnosis of diabetes. Diabetes prevention program and other research programs have demonstrated that escalation of prediabetes to the type 2 diabetes can be delayed by losing weight by diet and proper exercise.

Type 2 diabetes used to be called adult-onset diabetes and non-insulin dependent diabetes mellitus (NIDDM). This terms are not correct because children can develop this disease and some people may require insuli9 therapy.

3. Gestational Diabetes: - A temporary metabolic disorder that can develop in non-diabetic women during pregnancy, usually in third trimester. Family history of diabetes, excess weight and hormonal changes contribute to this diabetes. According to American diabetes Association about 4% of pregnant women develop gestational diabetes. Preeclampsia, premature delivery, oversized infant (macrosomia) and jaundice and breathing problem in occur in infant and mother may suffer some problem due to gestational diabetes. This disease ends with pregnancy but child and mother are at risk of developing type 2 diabetes later in life.

4. Secondary Diabetes: - Diabetes caused by another condition. Pancreatitis, cystic fibrosis, Down syndrome and hemochromatosis to medical treatment including corticosteroids, other immunosuppressive, diuretics and pancreatectomy are some of many potential sources of secondary diabetes. An uncommon disease caused by a genetic defeat inherited from a parent, it is known as Maturity-onset diabetes of young (MODY). Generallydiagnosed by the age of 25, in people of normal weight. MODY may be classified in type2 diabetes or secondary diabetes but considered a separate condition.

5. Wolfram Syndrome: - A genetic disorder that involves insulin-dependent diabetes, vision problems, deafness and diabetes insipidus.

6. Autoimmune polyglandular syndrome (APS):- Group of autoimmune endocrine diseases. Two of the three forms of this syndrome is features in type 1. Unstable diabetes, also known as brittle or labile diabetes, is term used to identify any case of poorly controlled diabetes regardless of type. Diabetes mellitus (sugar diabetes) involve all these condition. Water diabetes (Diabetes insipidus) is an endocrine disorder in which kidney release too much water.

Signs and symptoms of diabetes: -[3]

Sometimes no symptoms are experienced in some cases and diabetes may go undetected because its symptoms many attribute to another to many other causes.

Some symptoms and signs of diabetes include:-

- Polydipsia (Excessive thirst)
- Polyuria (Excessive urination) and dehydration
- Polyphagia (Excessive hunger or appetite)
- Unexplained weight loss
- Blurred vision, nearsightedness and other vision disorders
- Frequent infection like skin infection, thrush, gingivitis, urinary tract infections and yeast infection
- Slow healing of sores
- Skin problems, such as itchiness or acanthosis nigricans

- Fatigue, lethargy or drowsiness
- Shakiness or trembling
- Mood swings or irritability
- Dizziness or fainting
- Numbness, tingling or pain in feet, hands or legs,

Pathophysiology of diabetes:-

1. Type 1 diabetes: - it results due to the combination of environmental and genetic influences. It develops due to destruction of insulin producing beta cells of pancreas by body's immune system. Development of T-cell dependent autoimmunity in genetically susceptible individuals may be triggered by toxins or virus or dietary factors. Autoimmunity is manifested by detectable antibodies to ICA512/IA-2, insulin autoantibody, and glutamic acid decarboxylase.

Due to slow destruction of beta cells prediabetes may occur will develops into DM. Other autoimmune may also occur like Hashimoto's thyroiditis, Addison's disease and myasthenia gravis.[4]

2. Type 2 diabetes: - Main indicator of type 2 is insulin insensitivity because of insulin resistance, declining insulin production, and ultimately pancreatic beta-cell failure. Due to this glucose transport to liver, muscle cells and fat cells is reduced. Hyperglycemia occurs due to the increase in breakdown of fat. Hepatic glucose levels and glucagon rise during fasting are not depressed with a meal.Hyperglycemia results due to inadequate levels of insulin and insulin resistance. A large number of individual suffering from type 2 DM are obese with central visceral adiposity. Adipose tissue plays an important in pathogenesis of type 2 DM. Theory used to explain this link is the visceral hypothesis giving a key role in elevated non-esterified fatty acid concentration, two emerging therapies are ectopic fat storage syndrome.[5]

World scenario of diabetes: -

It is estimated that 366 million people had DM in 2011, by 2030 this number will be 522 million. 80% of people with dm live in low and middle income countries. Dm caused 4.6 million deaths in 2011. By year 2030, 439 million would have type 2Dm. Majority of DM cases in Africa is on type 2 with less than 10% of DM cases being type 1. A center for diseases control and prevention 2011 reports that Dm affects about 25.8 million people in USin 2010 with 90 to 95% of them being type 2.[5]

In 2000, India (31.7 million) was the country with highest number of DM cases followed by China (20.8 million) with US (17.7 million) in second and third place respectively. By 2030 DM may have affected 79.4 individuals in India, while in china 42.3 million and US 30.3 million people may be impacted by DM.[6]

Treatment of Diabetes

1) **Oral hypoglycemic drugs** [12]

Sulfonylureas: - Tolubutamide, Glipizide

Biguanides: - Metformin

Meglitinidies: - Repaglidnide

Thiazolidinedione: - Rosiglitazone

α glycosidase inhibitor: - Acarbose, Voglibose

Table 1: Oral Hypoglycemic Drugs[7]

Name of Drug	Mode of Action	Daily Dose	Route of Administration	Contraindication	Side effect
Metformin	activation of AMPK in hepatocytes	0.5-2.5g	oral	factors that predispose to lactic acidosis	Nausea, abdominal discomfort and diarrhea
Sulphonylurea	Stimulation of pancreatic β-cells	1mg-0.5g	Oral	liver disease	Hyperglycemia, Weight gain
Meglitinidies	Stimulation of pancreatic β-cells	1.5-480mg	Oral	chronic kidney disease	Hyperglycemia, Weight gain
Voglibose	they produce a reversible inhibition of membrane-bound intestinal alpha-glycoside hydrolase enzymes	50-100mg	oral	chronic intestinal disorders	flatulence, diarrhea and abdominal pain

2) Injectable agents

Table 2: Injectable Drugs.

Name of drug	Mode of Action	Daily Dose	Route of Administration	Contraindication	Side effect
Liraglutide [13]	Increase insulin secretion, Decrease in food intake and inhibition of post-prandial glucagon secretion	0.6-1.8mg daily	Subcutaneous	Thyroid cancer and Multiple endocrine neoplasia	nausea, vomiting, diarrhea, pancreatitis, hypoglycemia
Insulin [15]	Insulin stimulate glucose transport across cell membrane by ATP dependent translocation of glucose	0.2-1.6 U/Kg/day	Subcutaneous	Salbutamol; Oral Contraceptives, etc.	Hypoglycemia, Edema, Allergy
Dulaglutide [10]	It reduces rate of absorption and reduced renal clearance rate.	0.75-1.5 mg/week	Subcutaneous	Pancreatitis and are not approved for use in T1DM	nausea, vomiting and diarrhea

3) Metabolic surgery [10]

When Lifestyle management and medications do not achieve desired treatment goals bariatric surgery has emerged as the most effective treatment for attending significant and durable results.

Mechanism of action

the exact mechanism of effect of metabolic surgery on diabetes is not fully understood but many factors appear to play a role like change in bile acid metabolism, GI tract nutrition sensing, glucose utilization, insulin resistance and intestinal microbiota. This all factors lead to reduce hip Attic glucose production increased tissue glucose uptake improve insulin sensitivity and enhance beta cell function.[9]

Side effects

Myocardial infraction pulmonary embolism intestinal leakage bowel obstruction nutritional deficiency and rarely kidney stones alcohol abuse depression and suicide.[9]

Novel Technologies

Painless smart patch: The North Carolina state university have designed an insulin delivery devicebased on micro needle array patches. It is integrated with hypoxia sensitive hyaluronic acid (HSHA) vesicles containing insulin and glucose oxidase (GOx). It contains live beta cells and deliversinsulin when the level of glucose in blood increases. There are glucose responsive vesicles (GRVs)which are formed by the combination of HS-HA 2-aminoimidazoles, this complex forms theglucose responsive vesicles. Insulin and glucose oxidase is entrapped into the vesicles. Underhyperglycemic conditions, glucose undergoes oxidation catalyzed by GOx and this forms amicroenvironment of hypoxia which leads to dissociation of the vesicles and release of insulin.[8]

Advantage

1. Fast responsiveness and close similarity of pharmacokinetic parameters to pancreas
2. Ease of administration
3. Biocompatibility

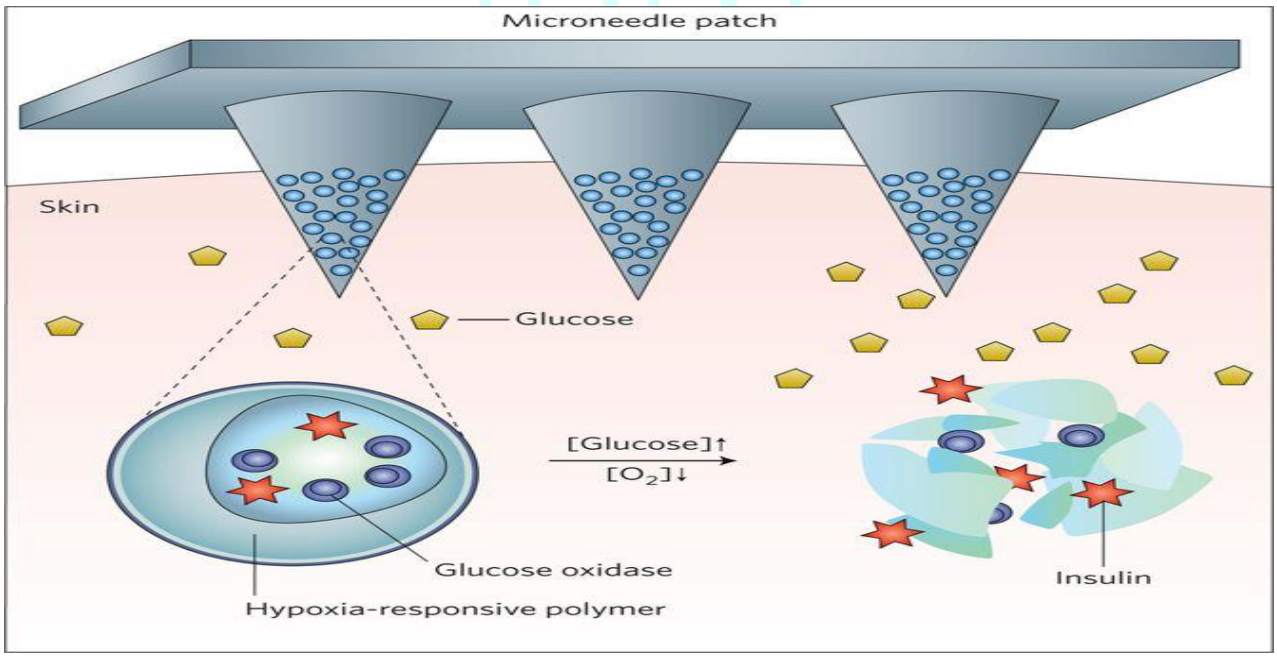

Fig 1: - Schematic of the glucose-responsive insulin delivery system using hypoxia-sensitive vesicle-loading MN-array patches[8]

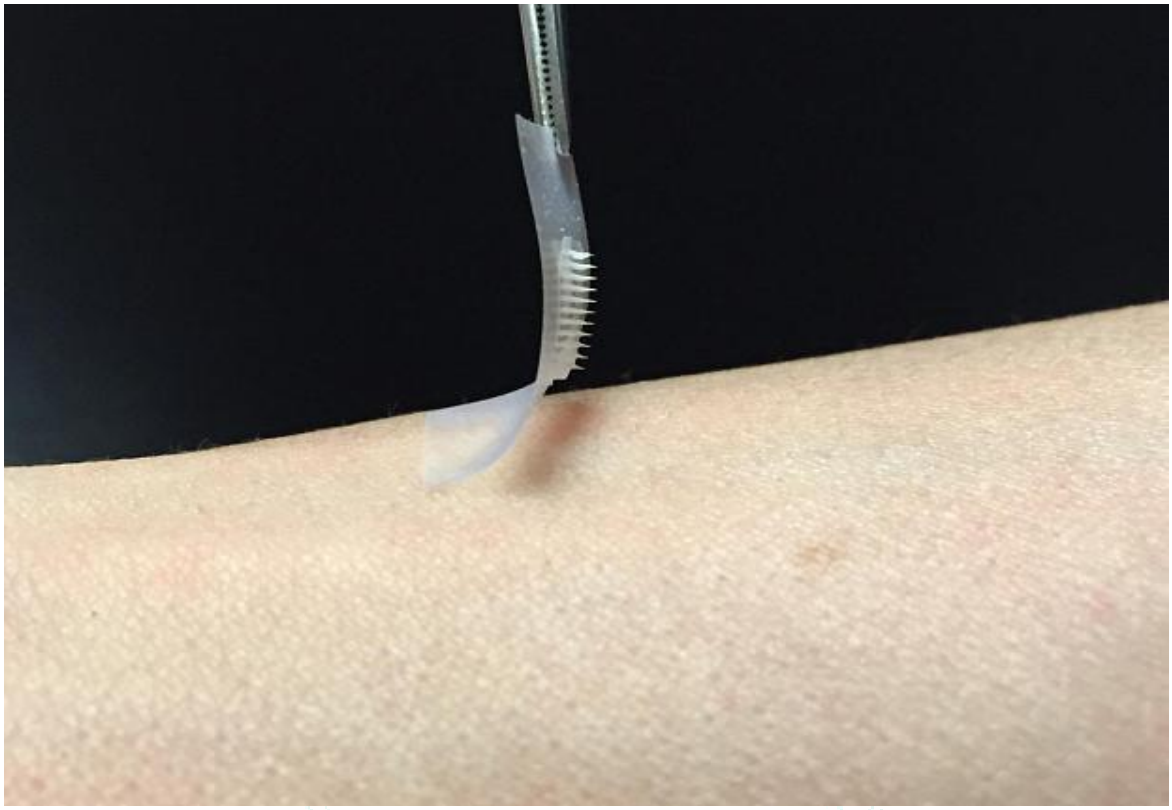

Fig 2: - Photograph of the smart insulin patch with an MN array

Clicksoft microinjection device: it is a spring loaded micro needle intradermal injectionsystem. Patient does not experience pain while administering insulin from this device. The patient,the micro needles project out of the device and pierces into the skin and the drug is passed into anultrafine needle in a fine stream of liquid medication from the drug chamber into the layers of theskin.[10]

Advantages

1. It has the proficiency to deliver 100 plus units of insulin in a single dose.

2. It has a faster onset of action when compared to any of the rapid acting insulin presentlyavailable in the market.

3. No refrigeration is required as it is using stabilized insulin.

4. Cost effective.

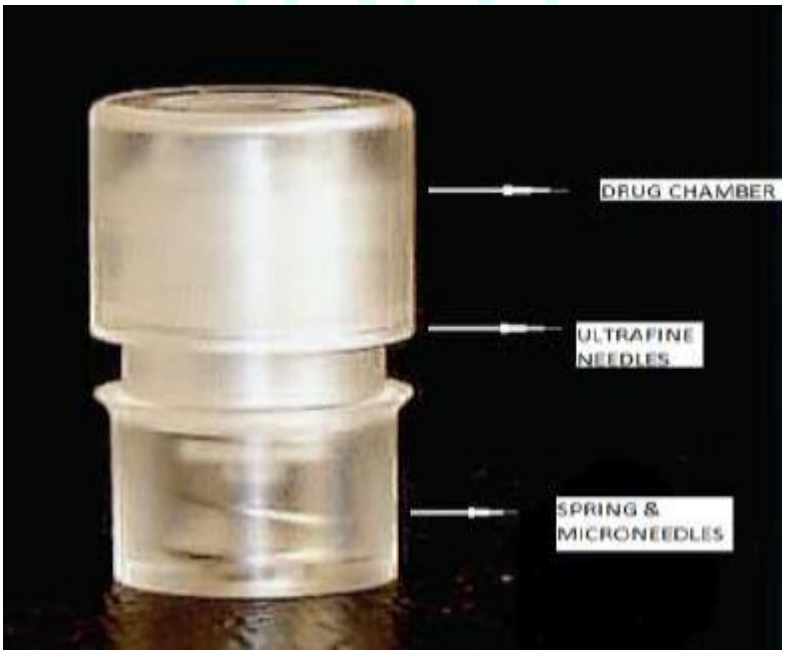

Fig 3: - Clicksoft Microinjection device with drug chamber[10]

Insulin pen: in this system a there is a pen which contains a cartridge of insulin and it can beused multiple times a day by a single patient using a disposable syringe every time. This devicereduces the risk of contamination between the patients. There are basically two types of pens thatis Prefilled pen and Reusable pen. Prefilled pens are "use and throw pen". Reusable pens are thosewhich have replaceable cartridges and once the insulin ends up the patient can insert a newcartridge. This system is economical but there are chances of loss of sterility. Needle is screwedinto the pen, then the dose is dialed, then injection is inserted subcutaneously and after pressingthe plunger the injection is kept inside for 5 sec. Generally, the capacity of these pens is 1.5ml or3ml. cartridge should be refrigerated and after it is inserted into the pen temperature should bemaintained.[8]

Fig 4: - Insulin pen[8]

V-go: It is a FDA approved device which delivers insulin every hour for an interval of 24hours. This system uses the patch technology and is non-electric and works without batteries ortubing. Vgo uses rapid acting analog insulin. It is waterproof. Every 24 hours a new insulincartridge has to be placed inside the device.[11]

Advantages

1. Needle phobia is eliminated.
2. Reduces multiple dose injections.
3. It can be taken outdoors
4. Adheres to the skin with colostomy adhesive.
5. Auto inserts 30 gauze needle that results to minimized pain

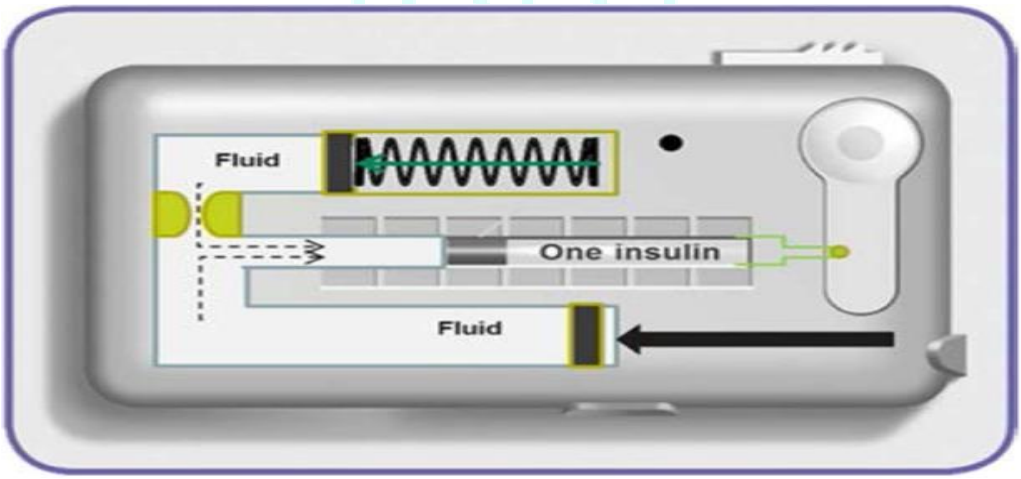

Fig 5: - V-Go device[11]

Afrezza Insulin Inhaler: Inhalation is appropriate route for the delivery of insulin because alveoli provideslarge surface area for rapid absorption of the drug into the blood stream. Afrezza is a product usedfor this purpose. It increases the absorption of glucose by the skeletal muscle and lessens theproduction of hepatic glucose. It is available with 4 and 8 unit cartridges which is tailored in theinhaler. The content of the cartridge comprises of dry powder of insulin which becomesaerosolized when the patient breaths through the inhaler.[8]

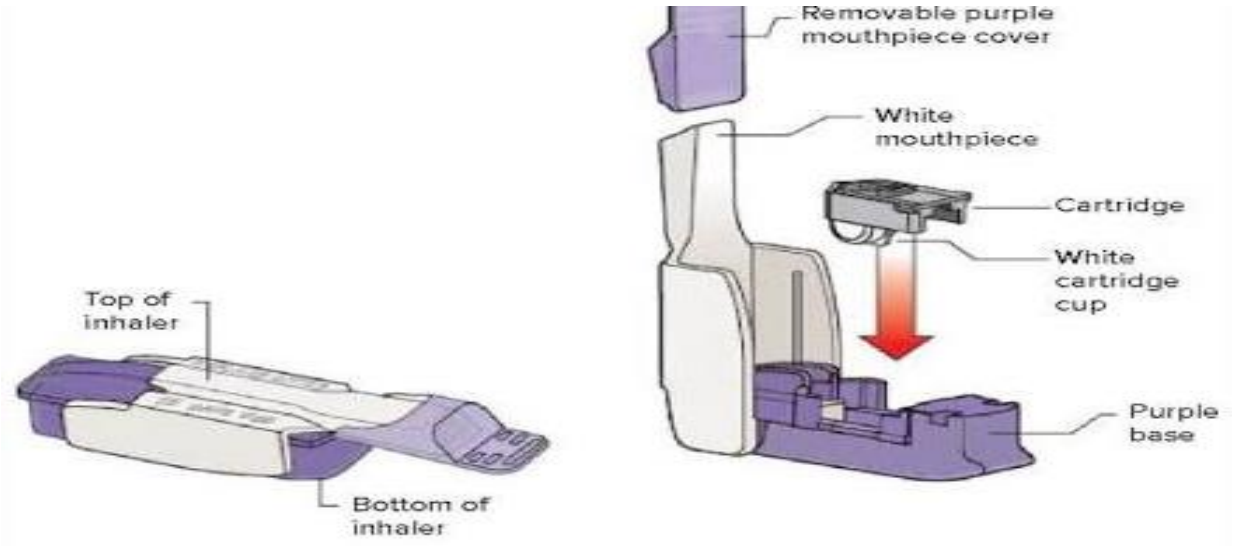

Fig 6: - Afrezza Pump.[8]

Alginate encapsulated pancreatic islets: Encapsulation of pancreatic islets offers an alternative to immunosuppression and the capsule act as semipermeable membrane that hinders the immune attack of the transplanted cells. Capsules are advantages over large device in that they provide Rapid diffusions of nutrients as well as oxygen and diffusion of insulin out to surrounding environment. Capsules reduce the risk of graft failure due to distribution of cell in numerous device. The capitals are normally injected into the peritoneal cavity where the cell get the access to nutrients and oxygen from the surrounding fluid.[16]

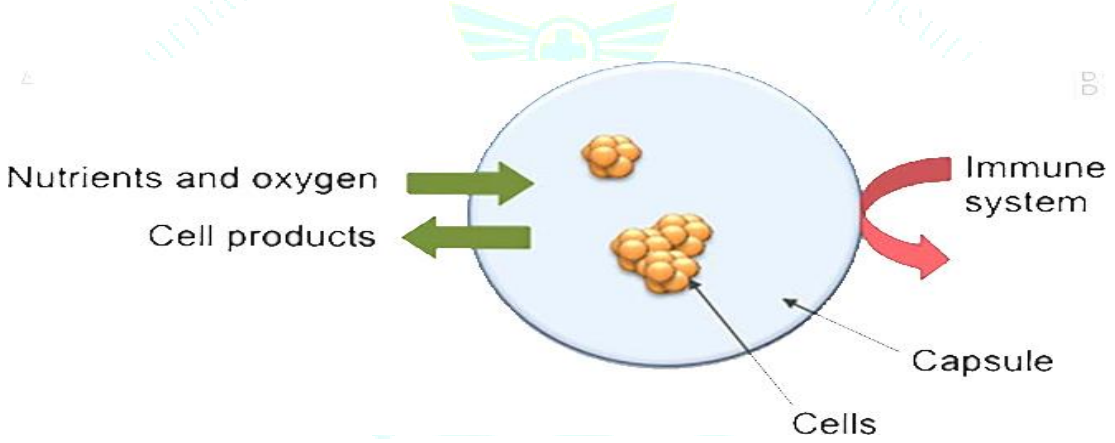

Fig 7: - Immune isolation by encapsulation. Demonstration of cells in capsule where nutrients and oxygen can diffuse into the capsule. [16]

Diagnostic test for Diabetes [14]

Table 3: diagnostic test for diabetes

Test	Criteria
Fasting Plasma Glucose (FPG)	≥126mg/dl
2-hr plasma glucose (during oral glucose tolerance test with loading dose of 75g)	≥200mg/dl
Casual plasma glucose (RPG)	≥200mg/dl
Glycated hemoglobin (A1C)	≥6.5%

Recent patented drugs for the treatment of diabetes [15]

Table 4: Recent patented drugs.

Generic/Code Name	Manufacturer	Indication	Phase
DPP-4 Inhibitors			
Dutogliptin	Phenomix/Forest Laboratories	Type 2 diabetes	3
Linagliptin	Boehringer Ingelheim	Type 2 diabetes	3
Melogliptin	Glenmark Pharmaceuticals	Type 2 diabetes	2
GLP-1 Analogs			
Albiglutide	GSK	Type 2 diabetes	2
Exenatide LAR	Amylin/Alkermes/Lilly	Type 2 diabetes	3
Taspoglutide	Roche/Ipsen	Type 2 diabetes	3
Biguanides			
Metformin gum/buccal	Generex/Fertin Pharma	Type 2 diabetes	2
Thiazolidinedione/PPAR-γ Agonists			
Balaglitazone	Dr. Reddy's Laboratories	Type 2 diabetes	3
Mitoglitazone	Metabolic Solutions Development	Type 2 diabetes	2
Netoglitazone	Mitsubishi Tanabe	Type 2 diabetes	2
Rivoglitazone	Daiichi-Sankyo	Type 2 diabetes	3
Selective Sodium Glucose CoTransporter Inhibitors			
Dapagliflozin	AstraZeneca	Type 2 diabetes	3
Remogliflozin	GSK/Kissei	Type 2 diabetes	2
Glinides			
Mitiglinide	Elixir Pharmaceuticals	Type 2 diabetes	3
Insulin			
Inhaled Technosphere insulin	Mankind	Type 1 and type 2 diabetes	3
Insulin intranasal	Bentley	Type 1 and type 2 diabetes	2
Oral HDV insulin	Diasome	Type 1 and type 2 diabetes	2
Oral insulin spray	Generex	Type 1 and type 2 diabetes	3
Rapid-acting insulin for injection	Biodel	Type 1 and type 2 diabetes	3
Recombinant human hyaluroindase for injection	Halozyme therapeutics	Type 1 diabetes	2

Future Prospects for Diabetes monitoring device

Sweat

Sweat can be easily accessed and its production can be stimulated on demand by Iontophoresis. Placing a sensor in close contact with skin sweat samples can be examined without contamination. A healthy person's glucose level were reported between 0.06 and 0.11mM while in case of diabetics it was 0.01 and 1mM. [17]

Wang ET Al have created a device that can be easily integrated into individual's lifestyle this device contains lactate biosensor connected on to the one of the nose Bridge pad. The device can be coupled by Bluetooth data to remove mobile host device for data analysis and visualization. [18]

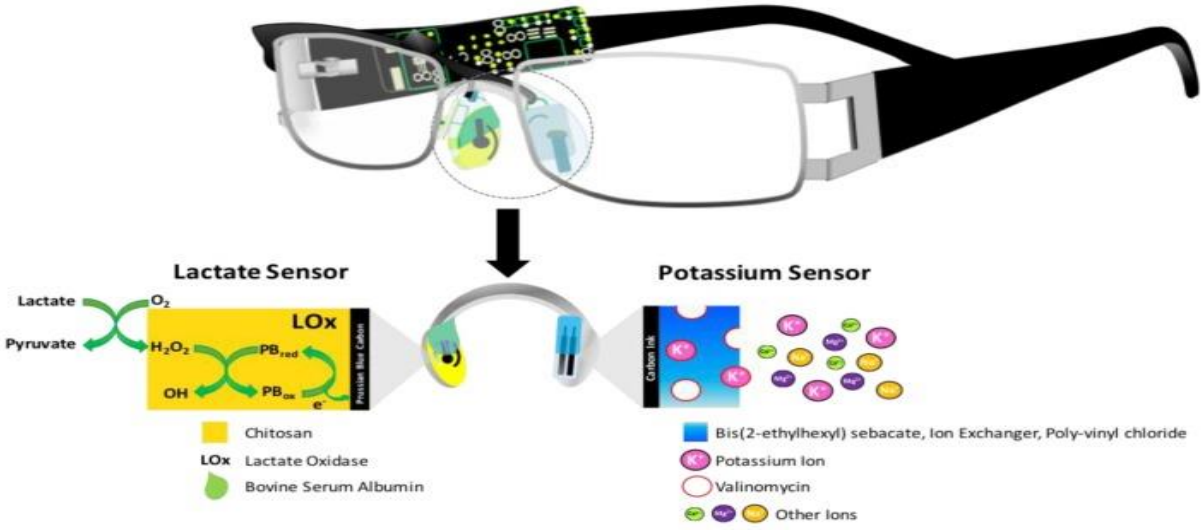

Fig 8: - eyeglasses biosensor system

Breath

Breath analysis is one of means for tracking the health status of an individual. Metabolism produces volatile organic compounds as a by-product they circulate around the body and pass over the alveolar interface and exhaled in the breath. Nano materials can be incorporated for sensing Acetone concentration in breath as an alternative to glucose monitoring for diabetes. The sensing units must have a high sensitivity to detect volatile organic compounds in Nano molar to Pico molar concentration range. [19]

Jiang and co-workers have reported a breath Acetone analyses which can detect Acetone levels in diabetic patient but the device requires the control external And Atmosphere in order to diagnosis diabetes accurately. [20]

Saliva

Saliva is a complex fruit containing many analytes that permeate from Blood there by providing a useful insight into a person's emotional, hormonal, metabolic and nutritional state. Saliva offers many advantages for diagnosis and everyday dental platforms like mouth guards' dentures as well as novel devices like dental tattoos which can be used for non-invasive detection of glucose in saliva. [21]

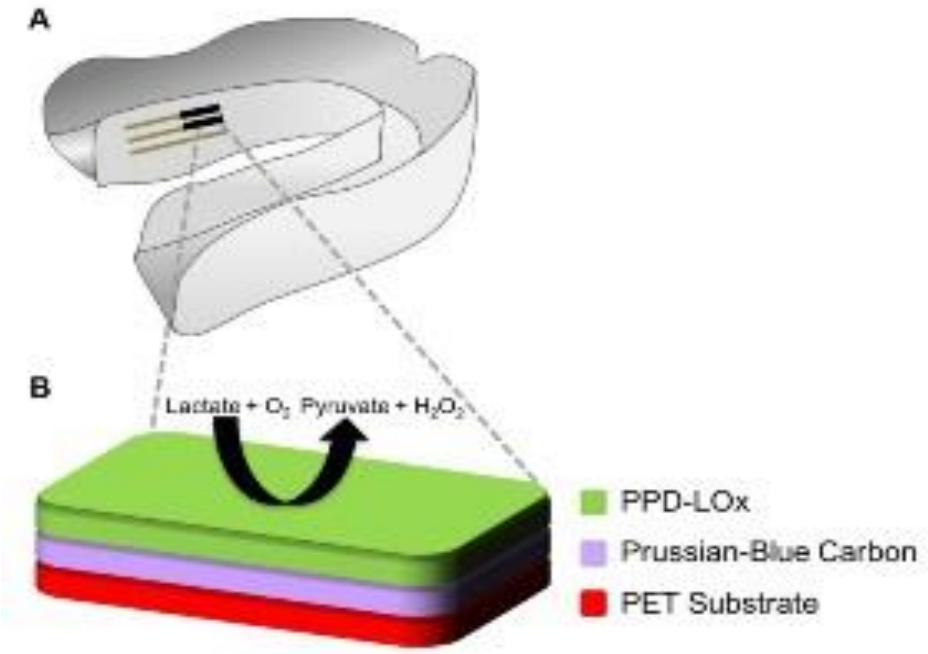

Fig 9: - Lactate sensing mouth guard[22]

Conclusion

Wearable sensors have the potential to play a major role in the continuous and non-invasiveMonitoring of biomarkers for diabetes. An important enabling step will be tocreate a clear understanding of the relations between the diagnostically relevant concentrationsof diseases markers in blood compared to other physiological fluids. Existing wearable devicessuch as fitness bands and smart watches, already dominate the market andprovide an information base that can be expanded to disease monitoring or diagnosis.However, these wearable technologies canprovide additional insights into the wearer's health and integrated in to clinical practices and promote actionable and behavioral change.

References

1. Akram T Khorrubi and Hisham M Darwish; "Diabetes Mellitus: the epidemic of century"; World journal of diabetes; 2015, June 25, 6(6), page no 850-867.
2. Kenneth S Polonsky; "The past 200 yeasr in diabetes"; The New England Journal of Medicine.
3. SamreenRiaz; "Diabetes Mellitus"; Scientific Research and Essay; Vol 4(5); May 2009; page no. 367-373.
4. Anees A Siddiqul, et al; "Diabetes: Mechanism, Pathophysiology and Management: A Review"; International Journal of drug development and research.
5. Abdulfatai B Olokoba, Et al; "type 2 Diabetes Mellitus: A review of current trends"; Oman Medical Journal; July 27(4); page no 269-273.
6. Seema A Kaveeshwar and Jon Cornwall; "The current state of diabetes mellitus in India"; The Australian Medical Journal; 2014, 7(1); page no 45-48.
7. Juan José Marín-Peñalver, et al; "Update on the treatment of type 2 diabetes mellitus"; World journal of diabetes; Baishideng Publishing Group; 2016 September 15; 7(17): page no 354-395.
8. Priya Raina, et al; "Novel Technologies Mark the Future of Insulin"; American journal of Pharmtech research; 2017; 7(1); page no 100-120.
9. Philip r. Schauer, md, et al; "metabolic surgery for treating type 2 diabetes mellitus: now supported by the world's leading diabetes organizations"; Cleveland clinic journal of medicine volume 84 • supplement 1 July 2017 page no s47-s56
10. Maneesh khaana, et al; "advanced delivery device- painless intradermal delivery system the novel Clicksoft microinjection; Drug Delivery Technology February 2009 Vol 9 No 2.
11. Rosemarie Lajara, et al; "Use of V-Go_ Insulin Delivery Device in Patients with Sub-optimally Controlled Diabetes Mellitus: A Retrospective Analysis from a Large Specialized Diabetes System" Diabetes Ther (2015) 6:531–545
12. KD Tripathi; "Essential of Medical Pharmacology"; Jaypee brother's medical publishers (P) ltd, Sixth Edition, Chapter-19; page no 254-274.

13. Mahamood Edavalath and Jeffrey W Stephens; "Liraglutide in treatment of type 2 diabetes mellitus: clinical utility and patient perspective"; Patient preference and Adherence; 2010:4; Dove press; Page no 61-68.
14. Habtamu Wondifraw Baynest; "Classification, pathophysiology, Diagnosis and management of diabetes mellitus"; journal of diabetes and metabolism; 2015; volume6; issue5; April 30, 2015.
15. Terri L. levien and E. Baker; " New drugs in development for the treatment of Diabetes"; Diabetes Spectrum; volume 22, number 2; 2009; Page no.92-105
16. BERIT L., et al.; "Current and Future Perspectives on Alginate Encapsulated Pancreatic Islet" STEM CELLS TRANSLATIONALMEDICINE 2017;6: page no1053–1058
17. Danielle Bruen, et al; "Glucose Sensing for Diabetes Monitoring: Recent Developments" Sensors 2017, issue 17.
18. Sempionatto, J.R.; et al. "Eyeglasses based wireless electrolyte and metabolite sensor platform" Lab Chip 2017, 17, 1834–1842.
19. Jiang, C.; et al. "A portable real-time ring down breath acetone analyzer: Toward potential diabetic screening and management" Sensors 2016, 16, 1199.
20. Yamada, K.; et al. "Measurement of natural carbon isotopic composition of acetone in human urine" Anal-Bioanal. Chem. 2016, 408, 1597–1607.
21. Bandodkar, A.J.; Wang, J. "Non-invasive wearable electrochemical sensors: A review" Trends Biotechnol. 2014, 32, 363–371.
22. Kim, J.; et al "Non-invasive mouth guard biosensor for continuous salivary monitoring of metabolites" Analyst 2013, 139, 1632–1636.