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CONSENSUS ON INSULIN THERAPY: REHABILITATION OF DIABETES

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ABSTRACT

Insulin is involved in regulation of glucose utilization in the body. Inability of the body to synthesize insulin or human cells resistance to insulin leads to a condition called Diabetes mellitus which is characterized by chronic hyperglycemia. There are two types of diabetes; type 1 and type 2. Exogenous supply of insulin is needed consistently for type 1 diabetes treatment and type 2 diabetes also needs to be cured by the exogenous supply of insulin in advance stages of the disease. Insulin Site of administration of insulin injection is equally important for better and safe action of insulin and can be given by intramuscular or intravenous route. Insulin replacement therapy is essential for anyone with type 1 diabetes. Most patients with gestational or type 2 diabetes may also require insulin. The goals of insulin therapy are: to achieve optimal glycemic control without causing hypoglycemia or excessive weight gain and to minimize the impact on lifestyle. The therapeutic goals should be individualized according to patient's age, disease duration, complications, comorbidities, lifestyle, and expected survival. Early insulins were extracted from the pancreas of pigs and cows but good glycemic control was difficult to achieve because of residual impurities after the purification process. The newer and purer animal insulins are better tolerated and can potentially achieve a level of glycemic control similar to synthetic human insulins. Clinically significant hypoglycemia rates between the human and animal insulins also appear to be similar. This review explores insulin in terms of its historical perspectives, regimens, adverse effect along with the future perspective.

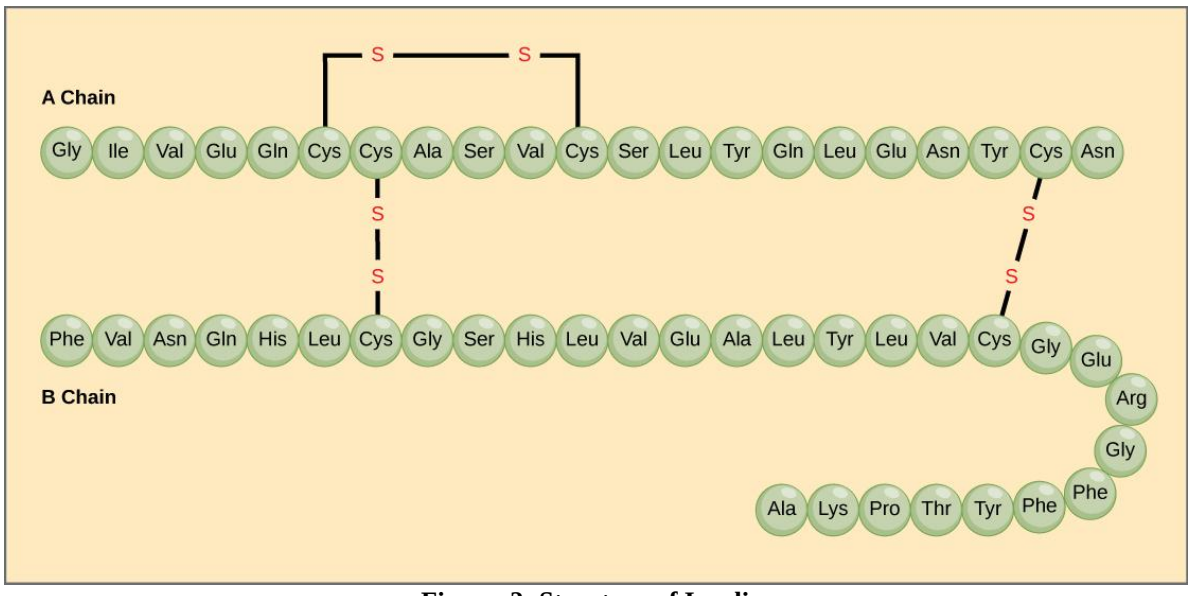
KEYWORDS: Diabetes mellitus, hyperglycemia, hypoglycemia, intravenous, intramuscular, purification process, glycemic control, DNA replication, Genetic engineering, Protein synthesis, Regime's, Immunogenicity, Glucose monitoring.

INTRODUCTION

Insulin is an important polypeptide hormone that regulates carbohydrate metabolism. Insulin is derived from the Latin word insula meaning "island" because the hormone is produced in the islets of Langerhans.[1]

Figure–1: Banting and Sanger [Nobel Laureates for discovery of Insulin].

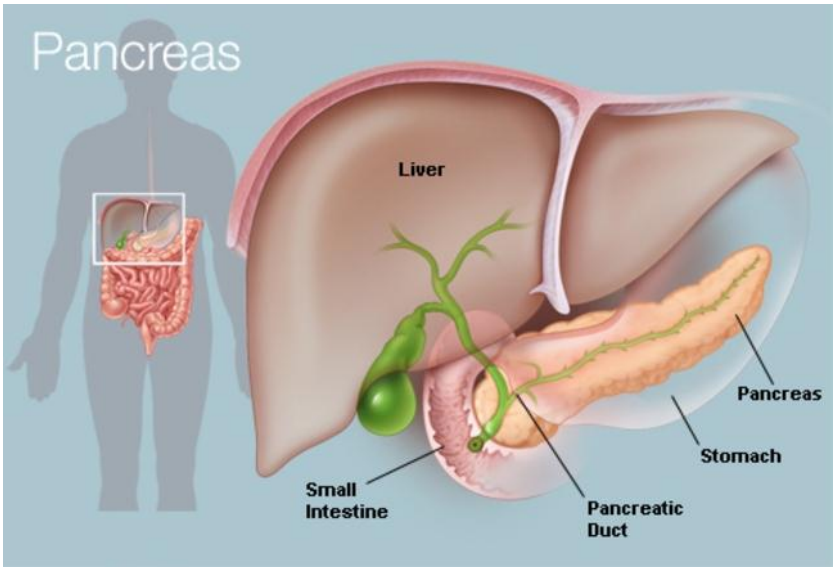
It was discovered by Banting and Best in 1921–1922 at the University of Toronto. It helps transport blood glucose into the body cells where the glucose is metabolized to produce energy. It maintains glucose concentration in the blood. When glucose concentration in the blood is increased, insulin lowers it by increasing glucose uptake by muscle, liver and fat cells. Excess glucose is converted to glycogen by these tissues. When glucose concentration is reduced in the blood, glycogen is converted back to glucose and released in the blood. It is involved in regulating amino acid uptake by increasing DNA replication and protein synthesis. Insulin facilitates fatty acid synthesis through the uptake of lipid from blood by fat cells. It also decreases, proteolysis, lipolysis and gluconeogenesis. Insulin is a potent anabolic hormone, and its absence induces a profound catabolic state that affects fat, carbohydrate and protein stores. Absolute insulin deficiency, such as that characterized by type 1 diabetes (T1DM), will result in death if left untreated. In this paper we highlight the developments of the past decade focusing on those technologies that show the most promise in improving the lives of people with diabetes, in particular, insulin pump therapy and real – time continuous glucose monitoring. In recent years, inhaled insulin has been an area of intense investigation; however, interest in this mode of insulin delivery has been diminished by concerns about potential pulmonary toxicity. A number of different insulin injection regimens are available for patients with type 2 diabetes who may already be treated with non–insulin–based therapies. These include a once daily injection of a long acting insulin, with an injection of a short – acting insulin with the main meal, twice a day injections of insulin mixtures, and multiple dose injections. Any insulin, once in circulation, will be degraded mainly by liver, which is responsible for approximately 60 to 80% of the total insulin disposal; approximately 10–20% is accounted by the kidney and the balance in the peripheral tissue. Insulin is a potent anabolic hormone essential for life. Insulin has a circulating concentration of 15 – 20 mU/L in the fasting state, and 60 – 80 mU/L post – prandially. Degradation of exogenous insulin also occurs in similar manner but since exogenous insulin is given subcutaneously, its onset of action and duration depends on rate of absorption. When insulin is replaced, our objective is to replicate meal–stimulated and basal insulin release by the healthy pancreas. Thus, insulin replacement regimens comprise of two components; a basal (fasting) and bolus (meal/prandial) insulin preparation. There are various insulin preparations developed to mimic normal insulin secretion pattern. Technological advances in medicine are highly anticipated and valued. As these advances gain recognition, they frequently change perspectives about appropriate treatments and may affect the information that physicians provide to families when discussing treatment options. However, it is imperative that newer treatments are evaluated to accurately identify treatment efficacy as well as possible psychosocial effects of treatment. These issues have been particularly relevant for children and adolescents with type 1 diabetes with the advent of the insulin pump.[2]



Figure–2: Structure of Insulin.

History of insulin development: A single protein (monomer) of human insulin is composed of 51 amino acids, and has a molecular mass of 5808 Da. The molecular formula of human insulin is $C_{257}H_{383}N_{65}O_{77}S_6$. It is a combination of two peptide chains (dimer) named an A–chain and a B–chain, which are linked together by two disulfide bonds. The A–chain is composed of 21 amino acids, while the B–chain consists of 30 residues. The linking (interchain) disulfide bonds are formed at cysteine residues between the positions A7–B7 and A20–B19. There is an additional (intrachain) disulfide bond within the A–chain between cysteine residues at positions A4 and A11. The A–chain exhibits two α–helical regions at A1–A8 and A12–A19 which are

antiparallel; while the B chain has a central α–helix (covering residues B9–B19) flanked by the disulfide bond on either sides and two β–sheets (covering B7–B10 and B20–B23) Insulin was the first treatment discovered for managing diabetes mellitus (DM) and still it is considered most effective. The history of insulin begins at the beginning of the twentieth century. In 1920, the pathologist Barron1 recognized that pancreatic duct obstruction causes atrophy of the exocrine pancreas while endocrine pancreas remains unaffected. This information was utilized by Frederick G Banting. He ligated pancreatic duct in dog and thus atrophy of acinar cells was induced and this led to isolation of islet hormones without their destruction by digestive enzymes. Insulin was finally discovered in 1921 by joint work of Frederick Banting, Charles Best, James Collip and JJR MacLeod. They received the Nobel Prize in 1923 for this discovery. On January 23, 1922 at the Toronto General Hospital, Leonard Thompson, a 14–year–old boy received the first dose of an extract from ox pancreas containing insulin and the injected material, which lowered his blood sugar. This was the first step towards insulin therapy. Only short–acting insulin was available in first few years after discovery. Efforts to prolong the action of insulin were initiated in 1923 and Neutral Protamine Hagedorn (NPH) insulin was first introduced in 1946 by efforts of Hagedorn. Hallas–Moller et al. of Novo Nordisk developed insulin zinc suspension commonly known as Lente insulin, another widely used intermediate–acting insulin. The NPH and regular insulin were combined to obtain premixed insulin. J Erik Jorpes (Sweden) showed that re–crystallization of insulin reduces allergy towards it. In 1970, chromatographically purified insulin was introduced using technology developed by Jorjen Schlichtkrull. The earlier soluble insulin preparations could be manufactured only at acidic pH, which was required to solubilize foreign proteins and protect insulin from degradation. With development of purification methods, it became possible to produce neutral insulin solution. Frederick Sanger first described the structure and amino acid sequence of insulin including species related molecular differences in 1955. He was awarded the Nobel Prize for this discovery in 1958. Berson and Yalow introduced the high sensitivity radioisotope method for detecting antigen–antibody complexes. This discovery led to the development of radio immunoassays and subsequent great strides in the field of endocrinology. For this discovery, Rosalyn Yalow received the Nobel Prize in 1978.The first commercially available human insulin was made by a biosynthetic method developed by Jan Markussen and associates of Novo Nordisk in 1981. In 1982, the first genetically engineered human insulin was introduced by Eli–Lilly as a result of work carried out in Genentech Laboratories using *Escherichia coli* as the host cell. Genetically engineered second generation human insulin was introduced by Novo Nordisk in 1984 using a method to produce a single chain insulin precursor using *Saccharomyces cerevisiae* as the host cell. Insulin therapy has significantly evolved since 1922, with major improvements in insulin purification, production, formulation, regimens, and delivery systems.



Figure–3: Pancreas.

To produce such insulin, pancreas is selectively picked, and deep frozen. Acid ethanol/water extraction ensures high solubility of insulin, low solubility of proteolytic enzymes and other proteins and provides protection against enzymatic degradation. The extract is then neutralized to remove unwanted pancreatic proteins, acidified again and evaporated to increase the rather low insulin content (0.02%), recover ethanol, and remove fatty substances. The next step is addition of 2–3 mol/L sodium chloride, a process commonly referred as salting out. This leads to separation of unwanted proteinaceous and non–proteinaceous compounds. The product is then subjected to purification process. Bovine insulin is extracted from cattle pancreas. It differs from human

insulin in three amino acids, namely A8, A10 and B30. Because of these differences even when purified it exhibits. Absorption is quicker and duration of effect is slightly shorter than bovine insulin but slightly longer than human insulin. Mixture of bovine and porcine insulin is more antigenic than single species bovine when both are purified to the same level. The pharmacokinetic profile is similar to bovine insulin.[3]

Animal Insulin: Animal insulin is not available now. But up to a decade ago, it saved millions of lives. Insulin from two animal sources was used, i.e. bovine and porcine, as meat from these animals is widely consumed. Earlier, no distinction was made between bovine and porcine pancreas and batches of insulin contained varying proportions of bovine and porcine insulin. The knowledge that porcine insulin had a molecular structure closer to human insulin and caused less immunogenicity, particularly when purified, led to the development of monospecies porcine insulin. To produce such insulin, pancreas is selectively picked, and deep frozen. Acid ethanol/water extraction ensures high solubility of insulin, low solubility of proteolytic enzymes and other proteins and provides protection against enzymatic degradation. The extract is then neutralized to remove unwanted pancreatic proteins, acidified again and evaporated to increase the rather low insulin content (0.02%), recover ethanol, and remove fatty substances. The next step is addition of 2–3 mol/L sodium chloride, a process commonly referred as salting out. This leads to separation of unwanted proteinaceous and non–proteinaceous compounds. The product is then subjected to purification process. Bovine insulin is extracted from cattle pancreas. It differs from human insulin in three amino acids, namely A8, A10 and B30. Because of these differences even when purified it exhibits antigenicity. subcutaneous administration, absorption is slower and its duration of effect is slightly longer than porcine or human insulin. Porcine insulin is extracted from pig pancreas. It differs from human insulin at only one position, i.e. the B30 position, hence is relatively less antigenic compared to bovine insulin. When purified, its antigenicity is quite low. Absorption is quicker and duration of effect is slightly shorter than bovine insulin but slightly longer than human insulin. Mixture of bovine and porcine insulin is more antigenic the single species bovine when both are purified to the same level. The pharmacokinetic profile is similar to bovine insulin.[4]

Human Insulin: Human insulin became available for treatment in 1981, initially as semi–synthetic, and a year later as the first genetically engineered product. Semi–synthetic human insulin or human insulin, as it was called earlier, was made by modifying porcine insulin, i.e. enzymatically replacing the B30 alanine with threonine, thus converting pork insulin to human insulin. Human insulin was the first genetically engineered protein used in therapy and its method of production is now widely used. Genetic engineering is a process by which genetic characteristics of a selected host cell (microorganism) are altered by inserting foreign DNA sequences (gene), which enable the host cell and its progeny to synthesize peptides encoded by the foreign gene. Genetic engineering is now being employed to produce a number of protein substances, which were earlier difficult to synthesize.[5]

Figure–4: Insulin.

TYPES OF INSULIN

Insulin release occurs both at a constitutive, basal rate and in short–lived large bursts, secondary to physiologic stimuli related to food intake. Thus, to replace insulin, there is need of insulin, which can rise rapidly in response to a meal as well as insulin which is released in circulation continuously at a slow rate. When insulin was discovered, for many years only regular or soluble insulin was available. Later prolonged action formulations were developed with protamine or zinc or both, as retarding agent, to delay absorption and extend the duration of effect. After advent of human insulin, animal insulin was losing its utility and hence animal insulins have been discontinued. Insulin analogs were

developed from 1995 onwards which resulted in discontinuation of lente and ultra–lente insulin. Thus, following types of insulin are now available:

Meal Time Insulins

- Regular human insulin
- Analogues (lispro, aspart, glulisine) Basal Insulins
- Intermediate: NPH, lente Analogues: Glargine, detemir Premixed
- Regular with NPH (30/70, 50/50, 25/75)
- Analog premix (30/70, 50/50, 25/75)

All insulin preparations have an international color code and color for a specific type of insulin is printed on vials and pen refills. Following table mentions characteristics of various available insulin preparations with their international color cod.[6]

Indications for Insulin therapy: The aim of diabetes treatment has changed with each new development and passing time. In the pre insulin era, the aim was to ensure that the patient had a less painful as no specific treatment was available. The discovery of insulin changed the aim to patient survival and prolonging life, by preventing acute complications, and subsequently also included making patients as asymptomatic as possible. The aim of treatment in the post Diabetes Control and Complications Trial (DCCT) era, has added prevention of complications and improving quality of life. In the 21st century, the aim of insulin therapy is gradually changing to provide physiological substitution and painless administration.[7]

Indications of Insulin therapy: All patients with diabetes have insulin deficiency in relative or absolute sense. As far as oral drugs are concerned, so many new drugs are added to armamentarium and thus now it is difficult to define oral antidiabetic drug (OAD) failure in type 2 diabetes. Thus, it is preferable to initiate insulin therapy if a patient with type 2 diabetes is not controlled on maximum doses of three oral drugs. It is actually beta cell failure rather than OAD failure. Insulin therapy is indicated for all women contemplating pregnancy, as well as for gestational diabetes. Regular, NPH, aspart, lispro and detemir insulin are approved to be used during pregnancy.[8]

INSULIN REGIMENS

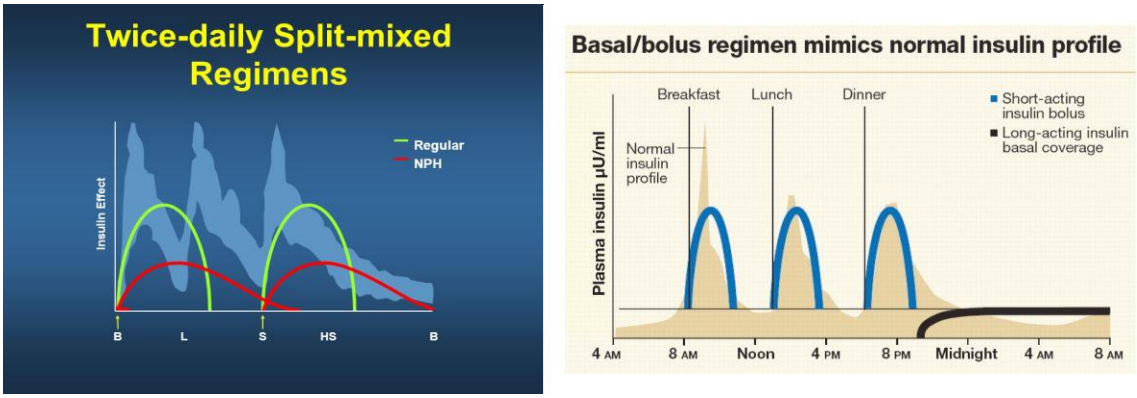
Physiological insulin release consists of basal and meal related secretion into the portal venous system which is precisely regulated as per glucose level in blood. There are many insulin preparations available to replace insulin in physiological manner. Each individual has a different pattern of insulin deficiency and insulin requirement.

Thus, there are many regimens of insulin replacement. First three treatment regimens are more often used. The choice depends on treat men goals, type of diabetes, pattern of insulin deficiency, meal pattern, dynamism of physician and motivation of patient.[9]

Basal Only Insulin Regimen: Basal insulin therapy goes back many years to bedtime insulin, daytime sulfonylurea (BIDS) insulin therapy, which added NPH insulin at bedtime to the only available oral therapy in the United States at the time. Another variation added 70:30 NPH regular insulin at suppertime. Another variant of basal only regimen in past was administration of one or two injections a day of an intermediate–acting insulin. Concept of basal only insulin regimen is now based on basal insulin analogs. After availability of basal analogs, basal only regimen often denotes one or two shots of long–acting basal insulin analog. Generally single injection of basal insulin is given daily, irrespective of meal timings. Since duration of action of basal analog is 24 hours, it is important that insulin should be given at the same time daily. Patient can do self–titration based on fasting glucose levels. Once fasting glucose is normal, prandial glucose monitoring is to be done.[10]

Premix Insulin Regimen: Mixtures in various ratios of soluble insulin from 10 to 50 are available, usually the 30:70, 25:75 and 50:50 ratio of short–acting to NPH is the most commonly used. In patients who have both basal and prandial insulin deficiency, premixed insulin formulations provide greater convenience as compared to basal–bolus regimen. Premixed formulations include a mixture of regular or rapid–acting analog in combination with NPH or neutral protamine analog insulin in various proportions. Premix insulin regimen can be conventional premix or analog premix regimen. Short–acting component of premix insulin is expected to take care of meal related glucose rise while intermediate–acting component is expected to take care of basal insulin requirements. Generally, premix insulin is given twice a day but it has been tried thrice a day also. Mixtures of 25/75 and 30/70 are traditionally dosed twice daily, usually two–thirds of the total daily dose before breakfast and a third of the total daily dose before supper. In patients taking two big meals, 50/50 premix is a better option. Premix insulin regimen have advantages with respect to convenience in administering the injection and disadvantages with respect to the inconvenience of having to be more rigid in the timing and composition of meals to achieve excellent control. In head–to–head studies, premixed insulin tends to reduce A1c to a greater degree than basal insulin alone, but at the expense of more hypoglycemia and possibly weight gain. Premix regimen is most popular insulin therapy in India as well as most other countries.[11]

Split Mix Regimen: Twice a day mixture of intermediate and short–acting insulin in the same syringe is split mix regimen. Major advantage is the fact that quantity of short and long acting insulin can be changed as per need. This is not possible with premix insulin regimen. Based on the self–monitoring, titration of insulin dose in split mix regimen can be done in the following manner:



Figure–5: Split–Mixed Regimen & Basal–Bolus Regimen.

- If fasting glucose is high, the dose of predinner intermediate–acting Insulin should be increased
- If pre–lunch glucose is high, the dose of pre breakfast regular insulin should be increased
- If post–lunch glucose is high, the dose of pre breakfast intermediate–acting insulin should be increased
- If predinner glucose high, the dose of pre breakfast intermediate–acting insulin should be increased. Split mix regimen cannot be used with pen devices.

Short–acting insulin has to be taken first in syringe followed by intermediate–acting insulin. This regimen is now a days often used by type1 diabetes patients who cannot afford basal–bolus analog therapy.[12]

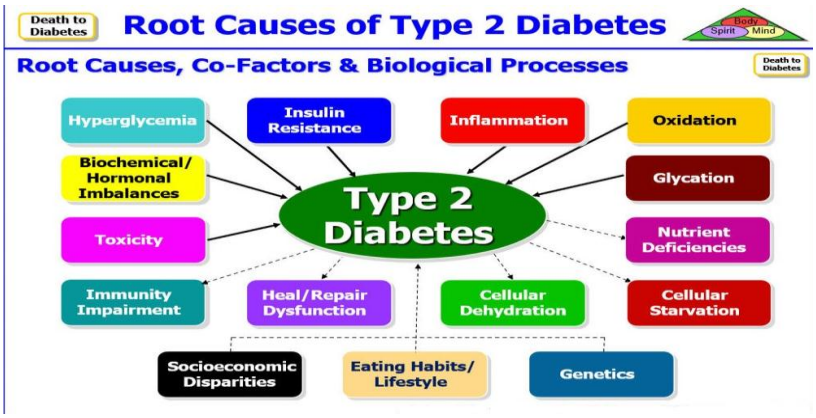
Basal–Bolus Regimen: This is also known as multiple subcutaneous insulin injections (MSII) regimen. It involves administration of intermediate–acting or long–acting insulin once a day as basal insulin together with regular or rapid–acting analog insulin prior to each meal, as bolus insulin. If basal insulin analog with rapid–acting insulin analog is used than this regimen is close to ideal. It is best suited for:

- Type 1 diabetes
- Young type 2 diabetics not at goal with premix
- Type 2 diabetes needing intensive glucose control
- People with brittle or labile diabetes
- Pregnant women with diabetes or women with diabetes contemplating pregnancy.

Selecting the most appropriate insulin regimen: Most people with T1DM and T2DM try a number of treatment regimens throughout their lives. There are many factors that influence the decision to opt for a specific regimen and ultimately the most important is patient choice rather than evidence from clinical trials.[13]

TYPE 2 DIABETES

While in some patients with T2DM insulin requirements are similar to those with T1DM, for many, insulin initiation and intensification is a more gradual process. Views differ on the insulin of choice for initiation, particularly as an add on to oral hypoglycemic therapy. Prior to the introduction of the long acting basal analogs, many patients requiring insulin were started on a twice a day premixed insulin often as an add on to metformin. If patients were also on a sulfonylurea this was usually stopped. Supported by clinical trials, using long – acting basal analogs as an add – on to existing oral therapy and low rates of hypoglycemia compared to those seen with NPH insulin, once a day long acting basal insulins are now recommended in T2DM treatment guidelines and have found significant popularity, particularly in the community as a means of introducing the patient to insulin. Anecdotally, while this is a popular way of starting insulin, many health care professionals struggle to achieve satisfactory glycemic targets with this regimen and many patients will require a second insulin injection with a meal time component within 6 – 12 months.[14]

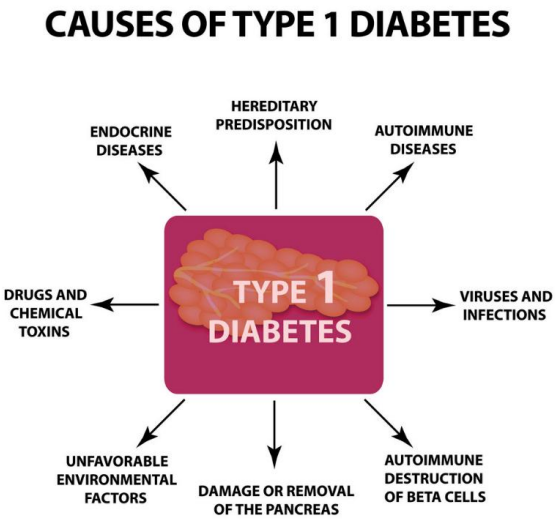


Figure–6: Causes of Type2 Diabetes.

Trials comparing twice daily premixed insulins with a long acting basal analog when added to metformin in insulin ï ve patients appear to show a benefit in favor of twice daily premixed insulin with respect to the numbers of patients achieving target HbA 1c values. The relative merits of basal only, prandial only and premixed insulin are unclear and are currently being further evaluated. Clearly, there are advantages and disadvantages associated with each approach. A pragmatic response is to consider each patient individually and their lifestyle, social circumstances and co – morbidities and taking into account what their insulin needs are likely to be in the longer term to make a clinical judgment. If it seems likely that if started on a basal insulin, they are likely to remain on this as a single injection or as part of a basal bolus regimen in the future, the basal insulin may be the best option. However, if it seems likely that the patient will be switched to a premixed insulin if a long acting bolus does not achieve target, then initiating with a premixed insulin would seem sensible. Starting the premixed insulin as a once a day injection increasing to two and sometimes three injections is also an option with some clinical evidence to 9support it.[15]

Type 1 Diabetes

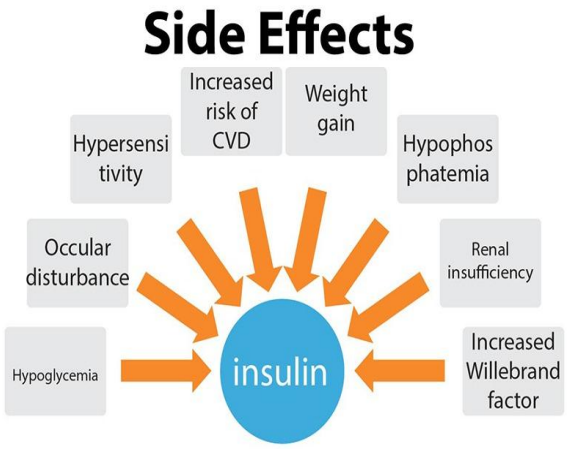
All patients with T1DM, unless they have been fortunate enough to become insulin independent following a pancreas or islet cell transplant, will require exogenous insulin to provide 24 – hour background and meal time coverage. For many patients this is provided by the basal bolus regimen. The advantages of such an approach are that it is generally better at providing a more physiologic insulin replacement with a greater degree of 24 – hour flexibility than less frequent premixed insulin. While it has the disadvantage of more daily insulin injections and for many more frequent self–blood glucose monitoring, which is not popular with some patients, particularly young and teenage children, it does provide a much greater degree of flexibility throughout the day. Importantly, it allows the patient to vary the meal time dose at up to three different time points during the day to accommodate different daily activities and meal sizes. For some, this "freedom" is less important and the administration of only two injections a day sways them towards an insulin premix.[16]



Figure–7: Causes of Type1 Diabetes.

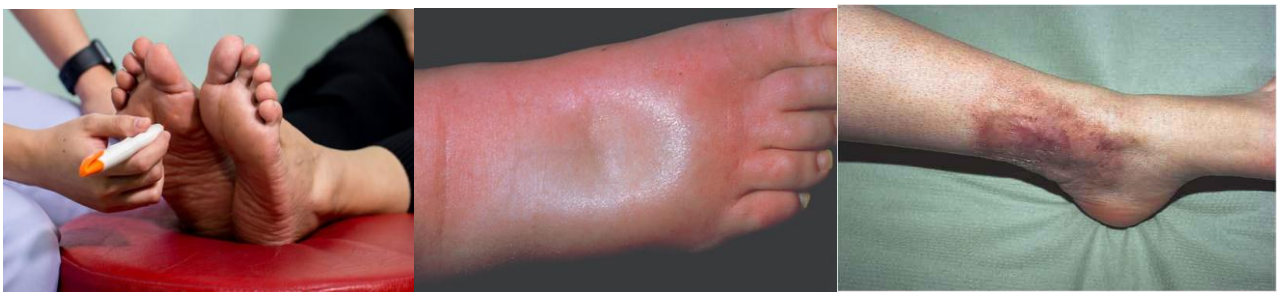
ADVERSE EFFECTS OF INSULIN

Hypoglycemia: Any treatment of hyperglycemia is likely to cause hypoglycemia so also with insulin. Hypoglycemia is the commonest problem with insulin therapy. There are a number of risk factors for hypoglycemia in insulin treated persons with diabetes. These include, excess dose, mismatched meal timings, and unusually vigorous exercise. Insulin dose has to be adjusted if there is no cause for hypoglycemia.



Figure–8: Insulin adverse effects.

Weight Gain: This is one of the limiting factors for glycemic control with insulin therapy. Appetite is increased with insulin therapy, which causes weight gain. Another factor is hypoglycemia and over–correction of hypoglycemia by eating large number of calories also leads to weight gain. The issue of weight gain has been looked at differently; as weight gain mainly occurred in those patients who had lost weight prior to effective insulin therapy and represented restoration of set–point weight.[17]



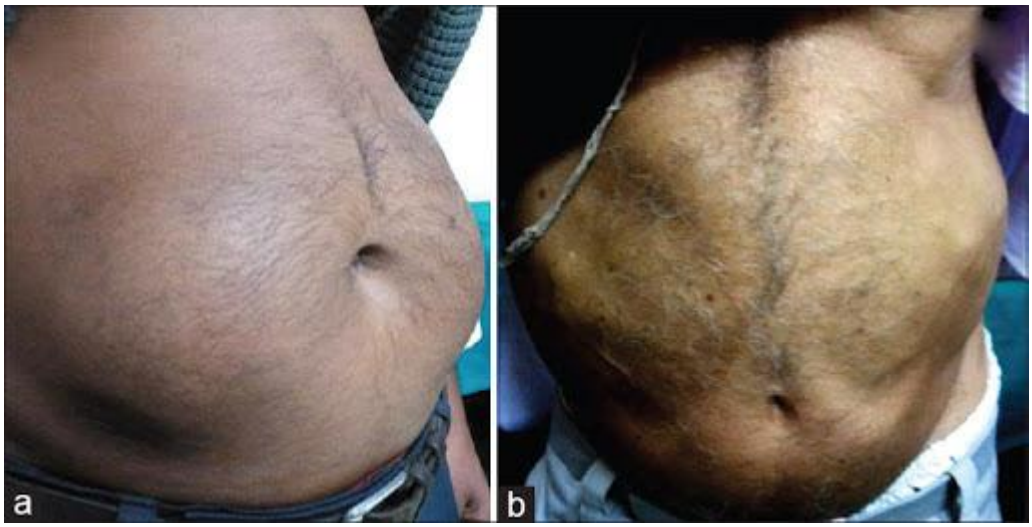
Figure–9: Insulin Neuritis, Insulin Edema and Insulin allergy.

Insulin Neuritis: Many patients develop a phenomenon of paresthesia when insulin is added. This occurs due to osmotic changes in nerve fibers. These symptoms are self–limiting and generally resolve in 4–8 weeks.

Insulin Edema: Water retention and edema occasionally develop when insulin treatment is started. Change in Vision On initiating insulin therapy and improvement in glycemic control, some patients experience changes in vision due to changes in the diameter of the eye lens as result of change in fluid content. This may require new pair of spectacles. The change in the spectacles should be made only after the BG stabilizes to the new level. A very rapid decrease in glucose levels in a patient with diabetic retinopathy may worsen retinopathy. Thus, in patients with significant retinopathy, glucose lowering should be slow.

Insulin Allergy: Immune response to injected insulin is determined by the type of insulin injected and the individual receiving it. Immunogenicity is determined by the species of insulin, its purity, pH, and presence of adjuvants. In the past, when impure insulin was used, allergy was very common. With widespread use of purified porcine and human insulin, the pharmacokinetic changes caused by insulin antibodies are becoming clinically irrelevant. There was a fear that these issues may surface again in relation to insulin analogs, however, despite the long–term use in large number of cases so far, the issue of insulin antibodies to insulin analogs has not caused any major concern or problem.[18]

Lipohypertrophy and Lipoatrophy: Use of less purified insulin results in unsightly depressions at the site of insulin administration due to atrophy of subcutaneous fat. It is not seen now a days as all insulin preparations are highly purified. More often seen problem is lipohypertrophy, which results due to insulin injection at the same site. Presence ofl lipohypertrophy makes insulin absorption slower and thus affects glucose control. It is very important to rotate injection sites to avoid lipohypertrophy. If lipohypertrophy is present, patient must be educated about injection site rotation and lipohypertrophic areas must not be used for insulin shots for nearly 2 months.[19]

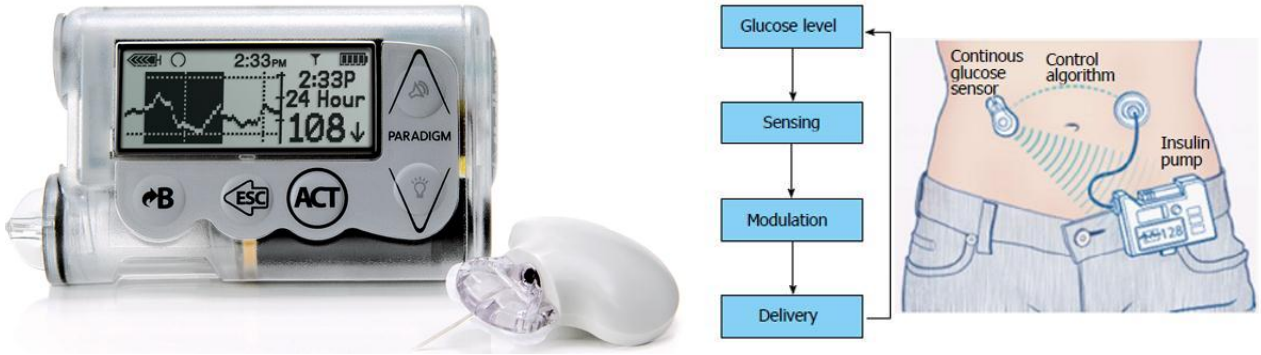


Figure–10: Lipohypertrophy and Lipoatrophy.

Controversial Issues

Cardiovascular Risk: Is insulin good or bad for the heart? To understand the issue of CV safety with insulin, Origin trial was conducted. Results were announced in 2012. In this study 12,537 patients (mean age, 63.5 years) with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes were randomized to receive insulin glargine (with a target fasting BG level of ≤ 95 mg) or standard care and to receive n–3 fatty acids or placebo. The median follow–up was 6.2 years. Rates of CV outcomes were similar in the insulin–glargine and standard–care groups. This study concluded that Insulin glargine has a neutral effect on CV risk.[20]

Cancer Risk: There are reports of cancer and CV risks with insulin therapy. A change in the structure of the insulin molecule relative to native human insulin is suspected to affect receptor interaction in unexpected ways. The binding capacity of insulin analogs to insulin–like growth factor (IGF)–1 receptor has been a matter of concern. Such binding may cause an increased residence time at the insulin receptor or an increased affinity for IGF–1 receptor may lead to increased mitogenesis, growth promotion and carcinogenicity compared to human insulin. An early analog that had these two properties B10 Asp (X10) was associated with carcinogenicity in female Sprague Dawley rats.[21]



Figure–11: Blood glucose monitoring.

A two–year study in female Sprague Dawley rats with insulin glargine showed no evidence of mammary gland tumors. This has been explained on the basis of the fact that the ability of insulin glargine to stimulate DNA synthesis in non–malignant cell lines with few or no IGF–1 receptor does not differ from that of human insulin. The safety of insulin glargine has clearly satisfied regulatory authorities in many countries around the world. In the Origin trial, there was no significant difference in cancers among glargine and standard care group (hazard ratio, 1.00; 95% CI, 0.88 to 1.13; P = 0.97). When used to target normal fasting plasma glucose levels for more than 6 years, insulin glargine had a neutral effect on cancers.[22]

WHAT'S NEW AND FUTURE?

Novel Insulin Analogues: The molecular structure of human insulin has been gradually refined over the past 2 decades, yielding several unique rapid–acting and long–acting insulin analogues with pharmacokinetic properties that closely imitate endogenous insulin profiles. Following are few of the many insulin analogs under development:

The insulin–PH20 (Halozyme Therapeutics) formulation contains one of the commercially available meal time insulin products mixed with recombinant human hyaluronidase (rHuPH20). Hyaluronidase makes insulin absorbed faster. Linjeta (Biodel) is another unique insulin formulation comprising regular human insulin with ethylenedia minetetra–acetic acid and citric acid. The latter additives act to chelate zinc ions and prevent self–aggregation of insulin molecules into hexamers on injection into the subcutaneous tissue, thus maintaining insulin in a monomeric state. As anticipated, Linjeta displays a faster onset of action and peak effect, with reduced intra–individual variability of metabolic action compared with regular human insulin and/or insulin lispro in healthy subjects and patients with type 1 diabetes.[23]

PEGylated insulin: Another novel approach to delay insulin absorption involves chemically coupling the insulin molecule to poly (ethylene glycol) PEG. A pegylated form of insulin lispro, with a flatter, extended duration of action, has been developed by Eli Lilly and is currently entering phase III trials. Degludec Plus (Rhyzodeg): Degludec is the first basal analogue which can have a premixed formulation with insulin aspart. Degludec in combination with Liraglutide, GLP1 analog is also underway which will be a novel combination expected to take care of both beta and alpha cell dysfunction as well as weight sparing glycemic control.[24]

Closed Loop Insulin Pumps: Continuous glucose monitoring with CSII has made it possible to have an insulin delivery like artificial pancreas. The first step towards this was development of insulin pump with auto suspend during hypoglycemia. Now work is going on to develop pumps, which will deliver bolus insulin as well as will modify basal rates based on glucose value

measured by sensor. These are called closed loop insulin pumps. Thus, insulin therapy can be optimized only when it mimics endogenous insulin secretary pattern. It is impossible to replace insulin the way beta–cells secrete.

Still, if insulin is replaced keeping type of insulin deficiency in a patient and then if the right insulin type and right regimen and right insulin delivery technique is chosen then near normoglycemia can be achieved.

CONCLUSION

Insulin and glucagon play important roles in regulating metabolism, including glycolysis, glycogenesis, glycogenolysis, gluconeogenesis, lipogenesis, lipolysis, and protein synthesis. Insulin appears to be primarily involved in regulation at peripheral sites, specifically muscle and adipose tissue. An increasing blood glucose, FFA and AA, gastrointestinal hormones and glucagon, growth hormone, cortisol, parasympathetic stimulation, insulin resistance and obesity are factors or conditions that increase insulin secretion. In contrary, hypoglycemia, fasting, somatostatin and α–adrenergic activity are factors decreasing insulin secretion. Incidence of diabetes is increasing at an alarming rate. Exogenous supply of insulin is needed consistently for type 1 diabetes treatment and type 2 diabetes also needs to be cured by the exogenous supply of insulin advance stages of the disease. The current sources of insulin will not be enough in the near future to provide insulin to the vast majority of patient specially in the poor countries. Hence, alternative production systems like plants need to be investigated to meet the demands of near future.

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