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ROLE OF ALPHA LIPOIC ACID (ALA) IN BLOOD SUGAR CONTROL

Dr. Munira Hussain and Pratibha Sharma*

Different types of agents are continuously exposed to the production of reactive species called as Reactive Oxygen Species (ROS) in human body which are also called free radicals. Free radicals transfer their free unpaired electron and cause the oxidation of cellular components. In order to counteract the harmful effects of such species, body has provided endogenous antioxidant systems or exogenous antioxidants which can be obtained from diet that neutralizes such species and maintains the homeostasis of body. Any imbalance between the free radicals and antioxidants leads to produce a condition known as "oxidative stress" that results in the development of pathological conditions like diabetes mellitus. Various studies reveal that oxidative stress increases the development of diabetes by a change in enzymatic systems like impaired Glutathione metabolism and increase in lipid peroxidation. Glutathione, catalase and superoxide dismutase are various biomarkers of oxidative stress in diabetes mellitus. Oxidative stress induced complications of diabetes include stroke, neuropathy, retinopathy and nephropathy. According to epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases other than hyperglycemia.

Insulin signaling is modulated by ROS by two ways, on the one side, in response to insulin; the ROS are produced to exert their full pathophysiological function. ROS have a negative regulation of insulin signaling on the other side, interpreting them to cause insulin resistance which is a risk factor for diabetes type 2. In-vivo studies show the role of hyperglycemia in the production of oxidative stress in diabetic patients leading to endothelial dysfunction in blood vessels. Increase in the levels of glucose and insulin along with dyslipidemia in diabetes patients leads to macroangiopathies leading to oxidative stress and atherosclerosis.

A variety of mechanisms in the body normally occur as a defence against oxidative damages. This prevents such damage as well as allows the use of oxygen for normal functions. Such antioxidant protection by endogenous antioxidants encompasses molecules and enzymes that neutralize free radicals and other ROS, as well as metal-binding proteins that sequester iron and copper atoms considered to promote certain oxidative reactions. The body also makes some other important antioxidant enzymes that assist in "recycling or regenerating", other antioxidants like vitamin C and vitamin E if they have been altered from their protective activity.

Exogenous antioxidants obtained from the diet play important role in the body defense management. These include vitamin E, vitamin C, beta-carotene and lycopene, and other phytonutrients, or substances found in fruits, vegetables, and other plant foods which provide health benefits. Vitamin C a water-soluble, and vitamins E a fat-soluble, are particularly effective antioxidants because they quench a variety of reactive oxygen species and rapidly regenerated back to their active form as they neutralize free radicals. Small amounts of these vitamins obtained from the diet provide a great deal of antioxidant protection.*

Foods, particularly fruits and vegetables are rich in healthy ROS scavengers. Of course, they are rich in fiber, vitamins and minerals, but then they also contains important chemical "antioxidants" like alpha lipoic acid (ALA), which is a kind of antioxidant. It is commonly found in eaten plant foods that scavenges free radicals, fights inflammation and slows down the aging process.

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But perhaps its most famous due to its use in treating diabetes naturally. Human body also makes a small amount of ALA on their own. However the concentration in our bloodstreams increases considerably when we eat a healthy diet. It is naturally abundant in foods like green vegetables, potatoes and certain types of yeast. Lipoic acid is similar to a vitamin so can also be man-made in a lab and can be taken as an anti-inflammatory supplement.

ALA also known as thioctic acid and α-lipoic acid contains an organosulfur compound derived from caprylic acid (octanoic acid). Organosulfur is an organic compound that contains sulphur often associated with foul odours, but a lot of other sweetest compounds known are organosulfur derivatives. Examples of sweet compounds are saccharin, which is an artificial sweetener, possessing caloric value and about 300-400 times as sweet as sucrose. Caprylic acid, another molecule commonly called octanoic acid. It is an eight-carbon saturated fatty acid. Its compounds are occurring naturally in the milk of various mammals, and as a small constituent of palm kernel oil and coconut oil. ALA is made in animals in general, and is essential for aerobic metabolism in cellular respiration. ALA is manufactured and obtainable as a dietary supplement in some countries and marketed as an antioxidant. In other countries it is available as a pharmaceutical drug.

Biosynthesis of ALA is done from the precursor to lipoic acid, octanoic acid, via fatty acid biosynthesis in the form of octanoyl-acyl carrier protein. A second fatty acid biosynthesis pathway in mitochondria in eukaryotes is used for the purpose of energy.

Enzymatic activity of ALA: Lipoic acid is cofactor for at least four enzymes systems:

- the pyruvate dehydrogenase complex
- the α-ketoglutarate dehydrogenase or 2-oxoglutarate dehydrogenase complex
- the branched-chain oxoacid dehydrogenase (BCDH) complex
- the acetoin dehydrogenase complex.

In the citric acid cycle two of these are turns nutrients into energy in many organisms.

Lipoic acid is present in every cell inside the body which helps to turn glucose into "fuel" for the body. Eating a packet antioxidant in diet plus potentially using ALA supplements can boost the amount circulating in the body. This shows far-reaching benefits in many studies. The most important function of ALA is fighting the effects on free radicals in the body, which are hazardous chemical by-products formed during the process of oxidation. Within the cells, ALA is converted into dihydrolipoic acid which confers a protective shield over normal cellular mechanism.

Oxidation normally takes place in the body over a period of time due to normal chemical reactions like eating or moving. However, exposure to environmental toxins and pollutants generates compounds that can become very reactive and damage cells. In response, abnormal cells grow and multiply, or it can also cause slowing in metabolic efficiency and changing neuron signalling.

Like other antioxidants, alpha lipoic acid can assist in slowing down cellular damage that is one of the original causes of diseases like heart disease, cancer and diabetes mellitus. It also works in the body to reinstate essential vitamin levels, such as vitamin E and vitamin C, along with helping the body to digest and utilize carbohydrate molecules while metabolizing them into usable energy.

Alpha lipoic acid also acts like a synergist with B vitamins, which are needed for converting all macronutrients from food into energy. It conjugates to protein molecules, enabling them to act as cofactors for several important mitochondrial enzymes.

An important feature that makes ALA unique is that it is both fat-soluble and water-soluble, unlike other nutrients like vitamin A or B vitamins, C, D or E that can only be properly absorbed with either one or the other. Evidently ALA acts as a "heavy metal chelator," which binds to metals which are also called toxins, in the body like mercury, arsenic, iron and other

forms of free radicals that build their way into the blood stream through air, water, chemical products and the food supply .

Alpha lipoic acid can increase how the body uses a very important antioxidant known as glutathione, and it might increase energy metabolism too which is why some athletes use ALA supplements for enhanced physical performance.

Health Benefits from Alpha Lipoic Acid

The lipoic acid acts as an antidote in oxidative stress and inflammation. It seems to fight damage done to the blood vessels, neurons, brain, and organs like the liver or heart. This means it proffers numerous benefits throughout the whole body, from naturally treating Alzheimer's disease to controlling liver disease.

As ALA is not a recognized essential nutrient, so no established daily recommendation is needed to prevent its deficiency. However, in general low antioxidants in general can speed up in the aging process, resulting in symptoms like a decreased muscle mass, weakened immune function, cardiovascular problems and memory problems.

Uses in Diabetes and Diabetic Complications:

Alpha lipoic acid can protect cells and neurons of hormone production sites, so offers protection against diabetes. ALA is considered an effective drug in the treatment of diabetic distal sensory-motor neuropathy, which evidently affects about 50 percent of people with diabetes. As a dietary supplement, ALA seems to help in improvement of insulin sensitivity and might also helps in prevention of metabolic syndrome, a term given to a cluster of conditions like high blood pressure, high cholesterol and body weight. Some evidence has also revealed that it can help in lowering blood glucose levels.

ALA is used to help alleviate complications and symptoms of diabetes occurring due to nerve damage, including cardiovascular problems, numbness in the legs and arms, eye-related disorders, pain, and swelling etc. It should be added in any diabetic diet plan to treat this common disorder. People who develop peripheral neuropathy as a side effect of diabetes can find some relief from pain, itching, burning, tingling and numbness using ALA, but studies show that high doses in IV form are most effective as in place of eating ALA-rich foods.

A major benefit of alpha lipoic supplementation in diabetics is its effect in lowering risk for neuropathic complications. It is found that around 25 % of people with diabetes develop cardiovascular autonomic neuropathy (CAN). CAN is characterized by decreased heart rate variability and is also associated with an increased risk of mortality in people with diabetes. Research suggests 600 milligrams a day supplementation of ALA or lipoic acid for three weeks significantly reduced the symptoms of diabetic peripheral neuropathy. Some doctors also choose doses up to 1,800 milligrams a day safely in diabetics under supervision.

Dosage Recommendations of Alpha Lipoic Acid

One should always keep in mind that taking more ALA supplements will not always offer better results. Side effects and risks factors of taking more however seem to be very rare considering its natural origin which also found in the body at all times. A low dose of 20–50 milligrams per day is found sufficiently beneficial for general preventative health care. However in clinical care a larger dose up to 600–800 milligrams per day are sometimes used in patients with diabetes or cognitive disorders which are not recommended for the general public. So, dosage recommendations differ evidently as per the purpose and the person to whom it is going to be given. Some general guidelines that are within the safe range are as following:

- 50–100 milligrams for antioxidant purposes in generally healthy adults
- 600–800 milligrams for patients with diabetes (divided into two doses, usually tablets are 30–50 milligrams each)
- 600–1,800 milligrams for patients with neuropathy and diabetic neuropathy (dosages

this high should only be taken under supervision of a doctor)

According to researchers, the amounts of lipoic acid available in dietary supplements (ranging in dosage from 200–600 milligrams) can be as much as 1,000 times greater than the amounts that could be obtained through any type of diet alone. Taking ALA supplements with a meal is believed to decrease its bioavailability, so most experts recommend taking it on an empty stomach or at least one hour before or after meal is better for the best results.

Some foods sources of Alpha Lipoic Acid

Food	Mcg/G Dry Weight	Ng/Mg Protein
Spinach	3.15	92.51
Broccoli	0.94	41.01
Tomato	0.56	48.61
Green Pea	0.39	17.13
Brussel Sprouts	0.39	18.39
Rice Bran	0.16	4.44

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Erratum

In Vol.5, No. 1, January-March 2017, Page 16 Article titled "Psychological Aspects of Diabetic Patients for an Educator to Appreciate" was misprinted under the Authorship of "Sasthi Chakroborty & Debasis Basu". The correct authors are:

"Mamta Subbam Mridual Das & Debajyogi Banerjee:. The error is regretted.

FORUM FOR INJECTION TECHNIQUE & THERAPY EXPERT RECOMMENDATIONS (FITTER), INDIA: THE INDIAN RECOMMENDATIONS FOR BEST PRACTICE IN INSULIN INJECTION & INFUSION, 2017: PART I

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1. Abstract:

Healthcare professionals in India frequently manage injection or infusion therapies in persons with diabetes. Patients taking insulin should know the importance of proper needle size, the correct injection process, complication avoidance and all other aspects of injection technique from the first visit onwards. To assist health care practitioners in their clinical practice, Forum for Injection Technique and Therapy: Expert Recommendations (FITTER) , India has updated the practical advice and made it more comprehensive evidence-based best practice information. Adherence to these updated recommendations, learning and translating them in to clinical practice should lead to effective therapies, improved outcomes and lower costs for persons with diabetes.

2. Keywords:

Injection technique, FITTER, Persons with diabetes, Insulin, FIT, Lipohypertrophy.

3. Introduction:

Diabetes and its complications impact the health, wellbeing and finances of individual and family. India and China lead the world with largest number of persons with diabetes (PWD). As per 2015 data, India had 69.2 million people living with diabetes, which is projected to reach 87 million by 2030 .

Recently, there has been increased emphasis on optimal insulin therapy and blood glucose control in Type 2 diabetes mellitus (T2DM). A few, however realize that correct insulin injection technique is as important in achieving glycemic goal, as the type and dose of insulin delivered . Incorrect choice of injection site, delivery devices and technique may modify insulin absorption

Parameters, leading to disconnect between maximum glucose load and peak insulin effect. This can lead to either glycemic variability or unexplained hypoglycemia, and subsequently compromised long term outcomes.

4. Forum for Injection Technique (FIT) India Recommendations

Diabetes management needs lifelong commitment from health care providers (HCPs) as well as PWD. Even among the literate patient groups, inclination to practice insulin self-administration is low. All injectable agents rely on correct injection technique for optimal delivery and effect. Physician awareness and willingness to convey this information can help promote correct injection technique among PWD and even other HCPs . To create recommendations regarding this, the first Indian recommendations for best practice in insulin injection technique

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were published by FIT India in 2012. An addendum was published in 2013 covering special populations and insulin pump infusion technique. To make FIT India more comprehensive, another addendum was published in 2014 with focus on injection meal time interval, methods for minimizing pain during injections, amyloidosis and adherence. Later, the FIT India 2.0 recommendations, 2015 were updated incorporating all additional information and evidence. An addendum to the FIT India 2.0 was published in 2016 with focus on insulin use in hospital indoor settings.

5. Need for Revision of FIT India 2.0 Recommendations

The FIT recommendations have addressed the interests of HCPs and PWD, and have improved health outcomes by ensuring correct technique and insulin delivery. However, recent advances in device manufacturing, newer research findings, and updated international guidelines demand renewed commitment to optimizing insulin injection practices. Numerous reports have described the reuse of insulin syringes, pens and needles by HCPs as well as patients, potentially exposing them to needlestick injuries (NSI) and blood-borne diseases. Therefore, it has become imperative to add best practices, specifically addressing the safe use of insulin devices. The sections on adverse safety outcomes of faulty technique and health education to both HCPs and patients on safe disposal of diabetic sharps and wastes need to be strengthened. Measures to enhance awareness of the good injection practices among HCPs, as well as patients, and section on addressing barriers of insulin injection therapy also needs to be updated.

6. Materials and Methods

To update these recommendations, literature search was undertaken looking for recent systematic reviews, metaanalysis and clinical surveys of insulin injection technique used for improving injection practice. Evidence statements were developed for the issues listed, following the process recommended by the FIT scientific advisory board, India. Specific wording of the recommendations and supporting information were collated, and a grading was allocated to the recommendations based on the evidence statements. The subsequent document was circulated to the board members and expert committee members from India, 11 South Asian experts and 22 members from Afro Asian Referee group before being finalised for publication.

6.1 Grading of the recommendations

The grading method by Frid et al. (2010) which includes the activities specific balance confidence scale for the strength of recommendation and 123 scale for scientific support, has been used to grade the evidence (Figure 1) .Certain recommendations, which are supported by manufacturer advice or drug authority guidance, have been ranked 1 in scientific support.

ABC Scale:	123 Scale:
Strength of Recommendation	Scientific support
A: Strongly recommended	1: At least one randomised controlled study
B: Recommended	2: At least one non-randomised (or no controlled or epidemiologic) study
C: Unresolved issue	3: Consensus expert opinion based on

Fig. 1. Grading criteria by Frid et al. (2010)

7. Insulin Injection Technique Practices

7.1 Global Experience

Worldwide Injection Technique Questionnaire (ITQ) survey, one of the largest surveys in diabetes, was conducted from February 1, 2014, through June 30, 2015. It involved 13,289 insulin-injecting patients from 423 centers in 41 countries. The survey focused on patient characteristics and practical aspects of injection technique. India contributed 1011 participants from 20 centres .

The key observations from this survey were as follows:

- Nearly 30% of participants used 4-and 8-mm needle lengths each, while 5- and 6-mm needles each were used by approximately 20%.
- 40% participants reused needles (pen/ syringe) 3-5 times.
- Lipohypertrophy (LH) was most common complication of injecting insulin, self-reported by 29.0% and found by HCPs in 30.8% of patients.
- Patients with LH had high glycated hemoglobin (HbA1c) (average 0.5%) than in patients without LH. A significantly higher LH was associated with incorrect rotation of sites and with needle reuse.
- Patients with LH had high frequency of unexpected hypoglycemia and glucose variability.
- Regular injection instructions in the past 6 months led to proper rotation of injection sites, but fewer than 40% of patients got such instructions.
- Many used diabetic sharps ended up in public trash and constituted high risk for NSI. These findings underscored the need for updation of recommendations, their dissemination and implementation.

7.2 Indian Experience

The Indian results of the ITQ survey were recently published in Diabetes Therapy, March 2017.

The key observations from this survey were as follows:

- Nearly 40% of participants used 4-and 5-mm needle lengths, 8-mm needles were used by approximately 16%.
- 80% participants reused needles more than 3 times or more.
- Lipohypertrophy (LH) was the most common complication of injecting insulin, self-reported by 26% and found by HCPs in 22% of patients.
- Patients with LH had higher glycated hemoglobin (HbA1c) than in patients without LH. A significantly higher LH was associated with incorrect rotation of sites and with needle reuse.
- Patients with LH had high frequency of unexpected hypoglycemia and glucose variability.
- Regular injection instructions in the past 6 months led to proper rotation of injection sites, but limited patients got such instructions.
- Most used diabetic sharps ended up in public trash and constituted high risk for NSI. Evidence from other studies offers similar insight into the current status of injection technique in India. A tertiary care setting reported significant gap between the insulin administration guidelines and current injecting practices. Results showed that appropriate storage of insulin vials, mixing insulin properly before injection, practice of hand washing were followed by only 75%, 49% & 70% respectively. Cleaning of the injection site, injecting with the proper skin fold, injecting insulin at 90° angle was practiced by 76%, 69% and 55% respectively. The majority of patients (91%) disposed needle and syringes directly into the garbage and public drainage system.

  These results highlighted the importance of education and counseling on proper injection technique to all PWD and their caregivers.

Injection Technique Recommendations

8. Barriers to Insulin Injection Therapy

Identification of barriers is a critical step toward successful diabetes self-management and takes place through a careful patient assessment. Barriers to initiating and adhering to insulin injection therapy include

a wide range of obstacles relating to PWD, providers, and health care systems. These barriers can be bridged by a systematic process of pre injection assessment and counseling.

8.1 Pre injection Assessment

Pre injection assessment and counseling should help to choose the correct injection regimen preparation, delivery device and dose, while encouraging acceptance of, and adherence to therapy. Open-ended, nonjudgmental questions asked by diabetes care providers can help PWD address their concerns and adopt effective solutions.

8.1.1 Clinical assessment

A thorough patient assessment should precede therapy initiation. Optimization of injection technique with respect to the individual patient needs is critical for the success of injectable therapy . Safe self-administration of insulin also requires assessment of the individual‘s cognitive and physical abilities to follow instructions and perform the injection technique (B3).

8.1.2 Pharmacological plan

Decide the appropriate insulin regimen and preparation, keeping in mind the potential need for intensification or de-escalation of therapy. Choice of preparation or delivery devices may depend on expected duration of insulin therapy.

8.1.3 Environmental assessment

It is essential to inquire about storage conditions of insulin injection supplies and cold storage facilities (B2) . Insulin pens can be used instead of vials in extremes of temperatures (C1).

8.1.4 Sociocultural sensibilities

Sociocultural sensibilities of the community should be respected. It is advised to discuss the site of injection beforehand in Indian women so that their sensibilities are not offended (B3).

Table 1: Pre-injection assessment Recommendations

- Patients should be encouraged to discuss their injection related concerns. B3
- Pre-injection measures should include a complete history and physical examination of the patient, including assessment of manual dexterity, cognitive capacity, health literacy, numeracy skills, visual acuity, anxiety, local infections, ulcers and scars. B3
- Type of insulin and type of device prescribed, storage conditions, method of refilling of injection supplies and disposal facilities should also be assessed. B2
- If cold storage facilities are inaccessible, prefer insulin pens over vials. C1

8.2 Pre injection Counseling

More than 25% of PWD may refuse insulin therapy due to psychological insulin resistance (PIR). The most pronounced reasons associated with PIR have been shown in table 3. In an Indian survey of 198 T2DM patients, the major factors contributing to PIR were found to be pain during injection, fear of injection or hypoglycemia, social stigma and lack of education. Psychological challenges may vary from person to person . Person-specific communication strategies are required to ensure acceptance of, and adherence to therapy. These strategies vary according to age group.

8.2.1 Children

Stress and anxiety developed after diagnosis of diabetes in childhood hinders parent’s ability to administer insulin or encourage children to self-administer insulin (A1). Proper education and demonstration of injection technique on a toy doll by HCPs

may help parents, caregivers and children to overcome anxiety and other issues (A3). Play therapy is a useful method of explaining injection technique.

8.2.2 Adolescents

In adolescents, several factors such as peer pressure, lack of seriousness, pain, frustration and weight gain may also lead to sub optimal compliance. It is important to help adolescents overcome any possible misconceptions related to insulin injection by sharing information and benefits of insulin administration with them (B2)

8.2.3 Adults

Proper education about the course of diabetes and the need to start insulin therapy at some time in the future is very important in all newly diagnosed adult PWD (A3). It is important to explore and acknowledge concerns of the patients.

8.2.4 Elderly

Geriatric PWD should be counseled about the course of diabetes and proper injection technique. Kuo 2016, in his study encouraged patients to try a mock self-injection before starting insulin. Group attenders who did a mock self-injection demonstrated greater insulin initiation rates . Limited dexterity, visual impairment, and hearing impairment are some of the common issues to be dealt in geriatric patients.

8.2.5 Needle phobia, Trypanophobia,Belonephobia and Diabetes Stress

Development of trypanophobia or needle phobia may be associated with lack of confidence that the demands of insulin therapy will be handled, a belief that insulin therapy equates to a personal failure and a perceived loss of control over life and injection related anxiety. A recent clinical practice guideline recommended exposure-based therapy (vs. no treatment) for managing children seven years and older and adults with high levels of needle fear. Psychological counseling and acknowledgement of patient‘s personal obstacles is recommended to overcome needle phobia (A2).

Table 2: Tips to win over needle phobia

• Patient’s personal obstacles should be identified and acknowledged (A2).
• Patient’s sense of personal control has to be reestablished with a brief trial of insulin therapy if he/she opts to continue injections (A2).
• Expeditious follow-up of dose adjustments is important once the injection has been restarted (A2).
• Psychological counseling should be considered for patients who are really needle-phobic (A2).

Table 3: Recommendations to address barriers

PWD Barriers	Provider Barriers	System Barriers
Fear of injection & needle • Educate that insulin is an effective therapy for diabetes(A3). • Choose shorter 94mm0 and thin needle as these are less painful(A2). • Educate the patient about occasional pain during injection (A3).	**Patient’s adherence &wish to prolong noninsulin therapy** • Educate PCP’s that insulin is the most effective treatment to manage blood glucose(A3). • Most PCP’s agreed that patient’s feel much better after starting insulin therapy (A2).	**Overburdened workload among providers** • More involvement by nurses and paramedical staff is needed in diabetes care.

Socioeconomic status • Insulin pen improve treatment adherence and reduced health care utilization. • 3 ml cartridges may be more economical for those who use smaller dose of insulin.	**Fear of hypoglycemia** • Teach how to identify ,treat and avoid hypoglycemia(A2). • Increased focused education by HCPs to family members and caregivers.	**Limited access to education** • Use simple, pictorial & audiovisual educational materials.
Fear of weight gain • Dietary restriction and exercise can prevent weight gain.	**Fear of weight gain** • Regular exercise • Explain use of insulin analogs as they may be associated with less weight gain. • Concomitant use of metformin, GLP-1RA, SGLT-2I's,where appropriate.	**Limited training of providers in injection technique** • Instruct on and demonstrate appropriate injection technique. • Educational toys such as dolls and pillows for trail injections.
Psychological resistance • Show empathy by addressing the patients emotional concerns first(A2). • Encourage patients to express their feelings about injecting(A3).	**Monitoring of therapy** • If bruising continues or hematomas develop, reassure patients and screen concomitant medication for overdose/ inappropriate use of antiplatelet agents. • Educate on injection technique and single use of needles. • If pain persists , evaluate their injection technique.	**Poor compliance** • Ensure regular visits of patients. • Encourage patients to update injection diary.
	Anxiety, fear & pain reducing strategy • Demonstrate correct injection technique and encourage them to self-inject (A3). • Use devices which hide the needle(A3). • Use vibration, cold temperature (A3).	

HCPs = Health care providers; GLP-1RA = Glucagon like peptide-1 receptor agonists; SGLT2Is = Sodium Glucose Co-transporter 2 inhibitors

9. Injection Storage

Specific storage conditions provided by the manufacturer should be followed. Insulin should be stored in a cool (below 30ºC), dark place and must be protected from extremes of temperature such as direct sunlight, kitchen, closed cars, green houses, top of the refrigerator and television (A3). Insulin pens and vials, which are not in active use, should be refrigerated, but not frozen (A1). Pens should never be stored with needles . In places where a refrigerator is not available, it is advisable to put the vial in a plastic bag, tie a rubber band, and keep it in a wide mouthed bottle or earthen pitcher filled with water.

9.1 Travel: Surface

If the outside temperature is >30°C, insulin should be stored in a flask with ice or in a proper container while travelling.

9.2 Travel: Air

While travelling by air, one should ensure that

- If time zone difference is 2 or more h, it may require a change in insulin injection schedule.
- Insulin should never be placed in the baggage hold of the plane. Always carry it along in cabin.
- The shelf life of insulin should be adequate for the duration of the trip.

Table 4: Injection storage: Recommendations

• Store insulin in use at room temperature (15–25°C) and discard 30 days after initial use or follow manufacturer's instructions. A1	
• Currently unused vials/refill cartridges (meant to be used in future) should be refrigerated. A1	
• Never freeze (frozen insulin should be thrown away). A1	
• Storage recommendations specific to the insulin formulation according to the manufacturer's instructions (package insert) are to be checked before use. A1	
• When storing pre-filled insulin syringes, store them with the needle pointing up. A3	
• Never use insulin beyond the expiration date stamped on the vial, pen, or cartridge that is supplied by the drug manufacturer. A1	
• Avoid extremes of temperature such as: A3	
➢ Direct sunlight ➢ Closed cars ➢ The top of a television	➢ Kitchen ➢ The top of a radiaton ➢ Green houses

10. Device selection and use

PWD can inject insulin using either syringes or insulin pens. Though the syringe is the primary injecting device used in India debate exists over the safest, most effective method of administering insulin. In general, Insulin pens are considered to be safer but their inappropriate use may lead to biological contamination of the pen cartridge. Since pens are easier to teach and use, they are frequently the choice for new insulin users. Each has its advantages as shown in Table 5.

A subcutaneous injection aims to deliver medication directly into the subcutaneous tissue without any discomfort or leakage. Ultrasound measurements reveal a mean skin thickness of about 2.2 mm. Multivariate analyses (of age, BMI, ethnicity and gender in adults with diabetes) demonstrate that variation in skin thickness is not clinically significant. Hence, there is no medical reason to recommend needles longer than 4–6 mm to either children or adults. Extremely lean patients should be using a skin fold to inject even with a 4-mm and 5-mm needle.

Clinical studies have also reported equal efficacy and safety/tolerability of shorter needles (4 mm) in comparison to longer ones. A randomised trial compared the efficacy and tolerability of 4-mm and longer needles (5 and 8 mm) in adult diabetes patients. In addition to providing equivalent glycaemic control and alleviating the risk of intramuscular injections, a 4-mm needle resulted in less painful injections and did not increase leakage events compared to longer needles. This study also reported that shorter needles were preferred by patients. Thus, shorter needles may obviate

psychological insulin resistance and thereby help improve patient adherence to insulin injection therapy.

Table 5: Advantages of insulin pen devices and conventional insulin syringes

Insulin Pen	Insulin Syringe
• More convenient insulin delivery • More accurate dosing • Less pain because of small gauge of needles • Less intrusive/socially more acceptable • More flexibility because of disposable or reusable option	• Can be used for preparation from different manufacturers • Syringe barrel can be chosen based on insulin dose • Patients can see the number and scale lines together to have accurate dosing • Allow use of split-mix regimes • Less expensive

10.1 Syringe and vial

The risk of intramuscular (IM) injection is likely to increase with longer insulin needles and lower BMI. 6mm insulin syringes are the shortest needle length available and should be used to minimize accidental IM risk. Shorter needles also help to reduce pain and even simplify the injection technique. Needles longer than 6mm are not recommended in adolescents or adults.

10.1.1 Syringe & insulin match

In India, insulin is available in the strength of U-40 and U-100 concentrations. U-200 and U-300 insulins are also available but only as pen. To avoid dosing errors, syringes that match the concentration of U-40 and U-100 concentrations must be used (A1). Insulin syringes of U-100 have an orange cover and black scale markings denoting two units each while U-40 syringes have a red cover and scale marking denoting one unit each. Intravenous (IV) syringes must never be used for insulin administration. Date of opening the vial should be written with a black marker pen and the same should be used within a month time.

10.1.2 Syringe needle length & size

Today needle lengths available for insulin syringes are 6 & 8 mm with 28-31 gauge sizes. Use of syringe needles in very young children (less than 6 years old) and exceptionally thin adults (BMI <19) is not recommended, as it increases risk of IM injections.

Table 6: The correct use of syringes

• Check insulin vial for type and expiry date (A1).
• Ensure that right insulin syringe is used with the right strength of insulin in use (e.g. U-100 vial with U-100 insulin syringe) (A1).
• During initial step of drawing insulin, the air equivalent to the dose should be drawn up first and injected into the vial (A3).
• If air bubbles are seen in the syringe, tap the barrel to bring them to the top and then remove the bubbles by slowly pushing up the plunger (A3).
• Mix cloudy insulin by rolling between the palms 20 times till the solution is mixed uniformly, but do not shake (A3).
• Syringes should ideally be used only once and never be reused (A2).
• Dispose used syringes safely after use (A1).
• The injection site should not be massaged (A3).

10.2 Pens and pen needles

Insulin pens come in two basic types: Durable insulin pens, where cartridge can be reloaded into the pen; and disposable insulin pens are preloaded with insulin and are disposed once emptied. The numbering on the pen dose dial and its magnification, amount of strength and dexterity required to operate the pen should be checked. Prior to prescription, the anticipated duration of insulin use also determines choice of durable or reusable pen.

10.2.1 Pen Needle length & size

Pen Needles are available in 32, 31 & 29 gauges . Choice of needle length (4, 5 & 6 mm) is important. While avoiding intradermal delivery, shorter needles alleviate the risk of IM injections (Table 7) .There is no need to raise a skin fold with a 4 mm needle, while injecting in the upper arm.

Table 7: Estimated IM injection risk by body site

Needle length (mm)	Thigh (%)	Abdomen (%)
4	1.6	0.3
5	4.7	1.1
6	10.0	2.8
8	25.0	9.7
12.7	63.0	38.0

A randomized controlled study in 274 obese (BMI ≥30) PWD showed that mean improvement in HbA1c levels with the 4 mm pen needle were 0.08% and 0.10% as compared to 8.0 and 12.7 mm pen needle respectively, within equivalence margins. However, the 4mm pen needle was less painful than the larger needles (P<.05), with similar leakage rates reported (A2). Although 4 mm pen needle is the needle of choice in all obese patients, a 5 mm needle may be acceptable (A1).

Table 8: Correct use of pen devices

- Priming of pen devices is essential (observing at least a drop at the needle tip) and should be done according to the manufacturer's instructions before each injection (A3).
- Pen devices and cartridges are for single person use and are never to be shared with others as this increases the risk of cross-contamination (A2).
- Pen needles should ideally be used only once, and never be reused (A2).
- Use of new needles each time reduces the risks of needle breakage in the skin, clogging of the needle, inaccurate dosing, and indirect costs (A3).
- Hold for 10 seconds after pushing the thumb button in completely or before withdrawing the needle. This ensures delivery of full dose and prevents the leakage of insulin (A1).
- Do not leave needles attached to the pen. This prevents entry of air and other contaminants into the cartridge. Moreover, leakage of insulin, which can affect the subsequent dose accuracy, is prevented (A2).
- The injection site should not be massaged (A3).

10.2.2 One-patient/one-pen policy

Insulin pens are approved for single-patient use only, and FDA indicates that even if a new needle is used, the PWD are at risk due to possible biological contamination in the pen cartridges. Therefore, insulin pen cartridges should never be shared between patients (A1).

10.3 Needle length recommendations for children, adolescents and adults

- Children, adolescents and adults should use 4mm needle with pens and 6mm needle with syringes (A2).
- Children, extremely lean and elder patients warrants the need of skin fold especially when using 5 & 6 mm needle but in children, adolescent & adults, an injection angled at 45º is required while using 6mm needle (A1).
- In adults, injection into limbs and slim abdomen warrants the need for a skin fold with needles longer than the 5mm (A2).
- Shorter needle should be given at a 90º angle to the skin surface (A1).
- No clinical justification is available for recommending needle length more than 4 mm for pen needles and 6 mm for insulin syringes in adults (A2).

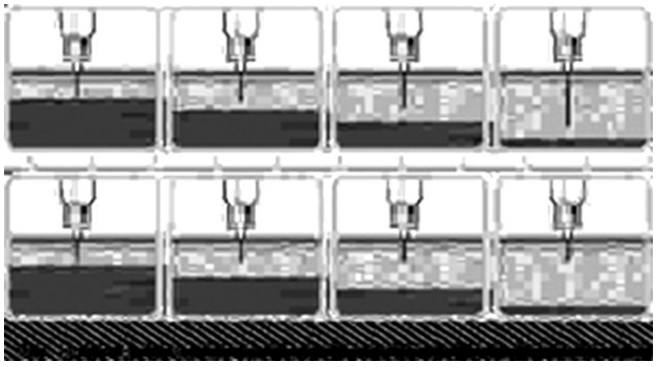

Fig. 2: Selecting the correct needle length: use of 4mm and 5mm needle length.

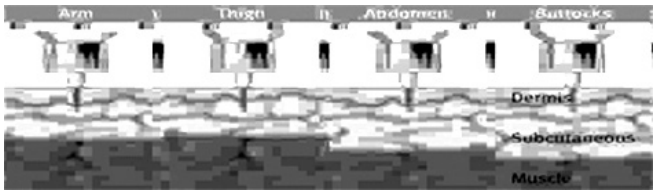

Fig. 2a: 4-mm needle appropriate for subcutaneous injection at all sites.

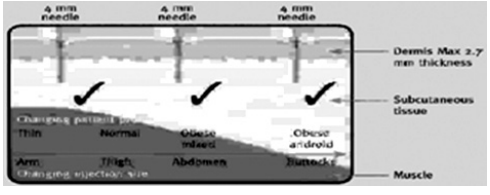

Fig. 2b: 4-mm needle.

Table 9: Needle length: Recommendations

Children and adolescents
• Children and adolescents should use a 4-mm needle with pens and the shortest needles available (currently 6-mm) with syringes (A2).
• No clinical reason exists to recommend needles longer than 6 mm in children and adolescents (A2).
• In children who are slim, when injecting into the limbs, a skin-fold is required: Especially when using a 5- or 6-mm needle (A1).
• An injection angled at 45° with a 6-mm needle can be used instead of a skin-fold (A1).
• If only an 8-mm needle is available, then they should lift a skin-fold and/or inject at 45° (A1).
• Injection into the arms needs third-party assistance and a lifted skin-fold for needle length more than 5mm (A3).
Adults
• Adults including obese patients can use 4-mm needle with pens, and 6-mm long needles with syringes (A2).
• Adults do not require the lifting of a skin-fold, particularly for 4-mm and 5-mm needles (A1).
• Shorter needles should be given in adults at a 90°angle to the skin surface (A1).
• An injection into the limbs or a slim abdomen warrants the need for a skin-fold with needles longer than 5-mm (A2).
• No clinical reason is available for recommending needles of length more than 6 mm in adults (A2).
• Patients already using needles ≥8 mm should move to a shorter needle or lift a skin-fold and/or inject at 45° in order to avoid injecting into muscle (A2).

11. Pre-injection readiness

Before preparation, insulin should be inspected for temperature, expiry date, possible damage to the bottle and possible spoilage of insulin. Ideally insulin should be at room temperature prior to injection (A3).

11.1 Cleansing

A knowledge, attitude and practice (KAP) survey from India, reported that 72.42% insulin user did not clean the injection site beforehand . Prior to injection, the site should be thoroughly cleaned either with cotton balls dipped in water or with alcohol swabs (A2). Cleansing should be started from the centre and then move outwards in the circular motion. Alcohol if used for cleansing should be evaporated completely, as the dry surface helps to minimize or avoid pain (A3). Do not use soap-based detergent, chloroxylenol, cetrimide/ chlorhexidine to clean prior to injection (A3). Insulin can be injected provided the site is considered 'socially clean.

Table 10: Cleansing

- Ensure that injection site is socially (one should be willing to touch the skin) clean before injection (A3).
- Recommend the use of alcohol swabs or cotton balls dipped in water for cleansing (A2).

11.2 Resuspension of cloudy insulin

A study conducted to evaluate how patients mix insulin before injecting showed that, only one person out of 180 patients could mix the insulin as per the manufacturers recommendation. In 58 out of 146 pens or cartridges (40%) the opacity of the insulin varied significantly from the expected value.

Neutral Protamine Hagedorn (NPH) or premixed insulin packaged in vials should not be shaken vigorously, but should be repeatedly inverted for about 20 times, till the suspension is uniformly clouded (A2). Failure to resuspend can lead to significant variability in action and particularly affects nocturnal plasma insulin concentration. The method of preparation is same for both reusable and prefilled disposable pens. In case premixed insulin is being used, insulin should be resuspended by rolling the pen and should not be shaken (A2). Correct resuspension technique has to be regularly evaluated.

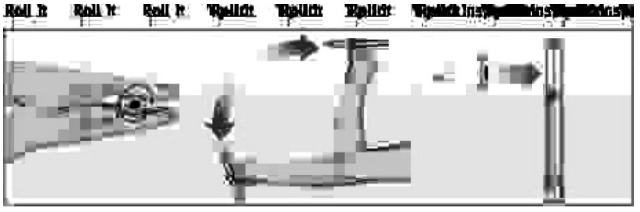

Fig 3: Cloudy insulin resuspension

Table 11: Injection device and insulin verification

- Emphasize the choice of injection device, needle length and gauge, and type of insulin syringe in the prescriptions (A1).
- Ensure that the pharmacist has dispensed the prescribed insulin. Check for: A1
  - Name and type of insulin
  - Expiry date
- Prior to use, it is critical to examine the insulin bottle and ensure there are no changes in insulin (e.g. clumping, frosting, altered colour or clarity) (A1).
- Clear insulin must be clear and cloudy insulin should be cloudy (A1).
- Resuspension of cloudy insulin is essential to ensure proper absorption. Vials and cartridges must be gently rolled and/or tipped (not shaken) for 20 cycles until the crystals go back into suspension (solution becomes milky white) (A2).
- Correct resuspension technique has to be regularly evaluated (A2).
- International colour codes can be used as an aid to identify insulin (B3).

11.3 Mixing Insulins

When short acting (regular) insulin is to be given simultaneously with intermediate acting insulin (NPH), they are usually mixed together in the same syringe. If admixtures which suit the patients insulin requirements are available commercially (premixed insulin), they should be preferred (A1).

Regular insulin should be filled first followed by NPH insulin (A3). Reversal of this order can contaminate the regular insulin vials (A3).Glargine insulin should not be mixed with any other insulin due to unique low pH of its diluents (A2).

Table 12: Mixing Insulins: Recommendations

- Patients who are well-controlled on a particular mixed insulin regimen are to maintain the same standard procedure for preparing the insulin doses (A1).
- Insulin glargine should not be mixed with other insulin forms because of the low pH of the diluent (A2).
- Rapid-acting insulin can be mixed with NPH insulin (A2).
- NPH and short-acting insulin, when mixed, should be used immediately (C2).
- If admixtures which suit the patient's insulin requirements are available commercially (premixed insulin), they should be preferred (A1).

11.4 Injection-meal time gap

Injection-meal time gap may affect the insulin efficacy. Hence, the timing of injection with respect to meal is critical in controlling glycemic levels (A1) . Patients should always follow physician's advice in this regard.

Short acting insulins should be administered 30 min before meal; whereas RAIAs can be injected before or immediately after a meal (A2) .

Intermediate acting insulins like NPH and long acting insulins like detemir and glargine should not be related to meal times and be injected at the same time every day. Ultra long acting basal insulin degludec can be injected at any time of the day, provided a gap of 8 to 40 hours is maintained between two injections . Co-formulation of degludec and as part should be injected with the main meal (s)of the day to provide both prandial and basal control .GLP-1 receptor agonist like exenatide is injected twice daily, 30 min before meals; whereas liraglutide is injected once daily, without regard to meal timings (A2). Coformulation of degludec and liraglutide (IDegLira) is injected once daily, at the same time each day.

Table 13: Injection-meal time gap: Recommendations

- Timing of insulin injection is critical for proper metabolic control (A1).
- The appropriate injection -meal time interval should be followed to enhance the glucose lowering effect (B2).

12. Injection Site and Technique

12.1 Choice of site

In ambulatory patients, the most commonly employed route for insulin administration is subcutaneous tissue. Other routes which are employed only during ketoacidosis or stressful conditions are IV, infusion or IM.

The presence of a fat layer and presence of only a few nerves in these regions makes injections convenient. The most commonly used sites for insulin injection are as follows: abdomen, upper arms, thigh and buttock.

12.1.1 Site assessment

The site has to be inspected by patient for inflammation, wounds or LH prior to every injection (A2) and systematically by HCPs at every visit or at least every 6 months (A3). Injection sites should be rotated systematically (A1).

12.1.2 Anterior abdomen

The site of choice for insulin injections is abdomen (A1). The space around a horizontal line drawn 2.5 cm above and below the umbilicus and lateral to vertical lines drawn 5 cm away from the umbilicus may be utilized for subcutaneous insulin injections.

12.1.3 Upper arm

Over the arm, the injection site includes the upper lateral mid third of the arm between the shoulder and elbow joint. Needle length more than 6mm warrants the need for a lifted skin fold especially in case of injection into the arm of the patients by a third party .

12.1.4 Anterior thigh

Over the thigh, the preferred site is in the anterior and outer aspect of the mid third of the thigh, between the anterior superior iliac spine and knee joint. If there is risk of nocturnal hypoglycemia, evening dose of insulin (NPH) should be injected into the thigh or buttock as these sites have slower absorption (A1).

12.1.5 Buttock

The upper outer quadrant of the buttock should be used. The upper outer quadrant may be located by placing index finger on the iliac crest and making a right angle between the index finger and the thumb. This site is not used routinely in adults. It can be used in infants and toddlers.

12.2 Injection site rotation

Systematic switching of the injections from one site to another site and within the injection site is important as it helps maintain healthy injection sites, optimizes insulin absorption and reduces the risk of LH (A1) . Use same site at the same time each day and rotate injection site to avoid glucose variability and LH (same time same site rule).

Administer insulin injections using a new injection site for each injection, in a systematic manner while ensuring stable insulin absorption. A common and effective scheme is to divide the injection site into quadrants (abdomen) or halves (thighs, buttocks and arms). One quadrant or half should be used for 1 week and then move either in a clockwise or an anticlockwise fashion to another quadrant or half, next week (A3). New injection site should be at least 1 to 2 cm apart from previous site (A3). Do not inject in the area of LH, inflammation, oedema or infections (A2). The HCPs should review the site rotation scheme with the patient at least once a year (A1).

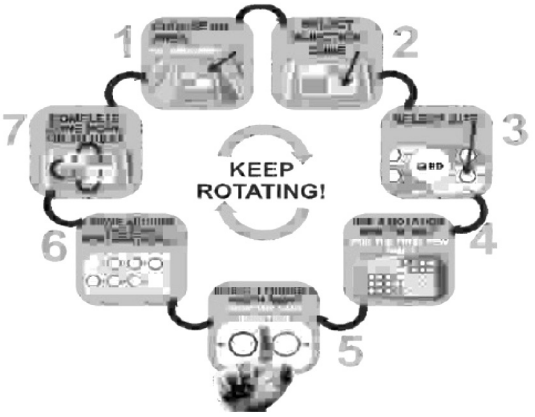

Fig 4: Correct site rotation

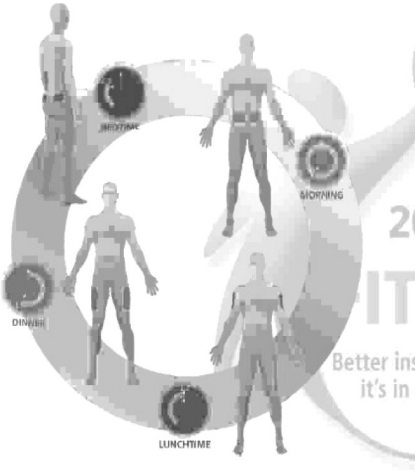

Fig 4a: Organized site rotation scheme

Fig 4b: Rotation sites.

Table 14: Rotation of injection sites

- An easy-to-follow rotation scheme should be taught to the patients from the onset of injection therapy (A2).
- Dividing the injection site into quadrants (or halves when using thighs or buttocks), using one quadrant per week and moving always in the same direction, either clockwise or anticlockwise, has been proven to be effective (A3).
- Injections within any quadrant or half should be spaced at least 1 or 2 cm apart to avoid repeat tissue trauma (A3).
- Rotation scheme should be audited during every visit and advice is to be provided where needed (A3).

12.3 Skin fold

Skin-folds are considered when the presumptive distance between the skin surface and muscle is less than needle length (A3). Ideally, the thumb and index finger are used to lift a skin-fold properly (possibly with the addition of the middle finger). Use of whole hand while lifting the skin risks lifting muscle and can lead to IM injections. Correlation between needle length and skin fold has been described in an earlier section of this recommendation.

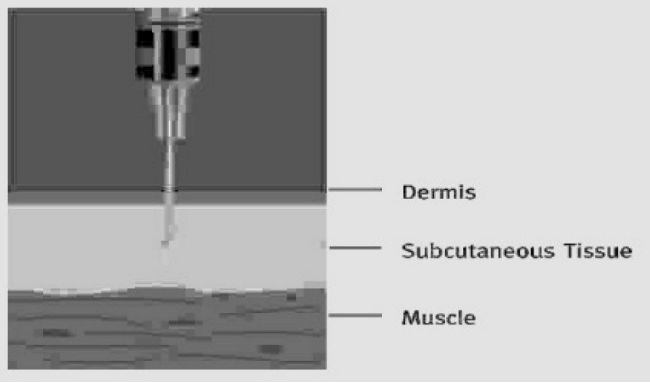

Fig 5a: Layers of the skin.

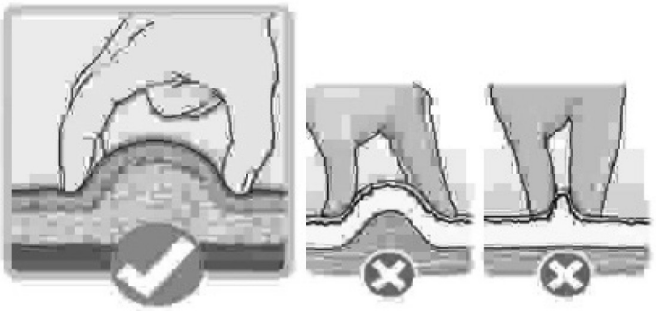

Fig 5b: Correct and incorrect ways of performing a skin-fold.

Table 15: Lifting skin-folds

- Injection site should be examined to decide whether lifting a skin-fold is necessary for the given length of needle (A3).
- The recommendation should be provided to the patient in writing (A3).
- People with diabetes and caregivers should be taught the correct technique of lifting the skin-fold from the onset of injectable therapy (A3).
- The lifted skin-fold should not be squeezed so tightly as to result in skin blanching or pain (A3).
- Indenting the skin should be avoided, as it makes needle penetrate deeper than intended (B3).
- The optimal sequence to perform a lifted skin-fold should be: A3
  - ➢ Make a lifted skin-fold
  - ➢ Insert needle into the skin at 90° angle to administer insulin
  - ➢ Leave the needle in the subcutaneous tissue for 10 sec after the plunger has been fully depressed
  - ➢ Withdraw needle from the skin and Release skin-fold
  - ➢ Dispose of the used needle or syringe safely

12.4 Injection technique (Optimal sequence)

- A lifted skin fold must be used if necessary (A3).
- Push the needle at a 90-degree angle into the skin.
- For lean patients, combined use of a raised skin fold and angled insertion is done.
- Avoid indenting the skin during the injection, as the needle may enter the muscle (B3).
- Administer insulin slowly & withdraw syringe needle at the same angle (A3).
- Hold the needle under the skin for at least 10 seconds after the plunger has been depressed (A1).
- Release skin fold (if done).
- Dispose off used needle safely (A3).

The steps of injection technique have been shown in table 16

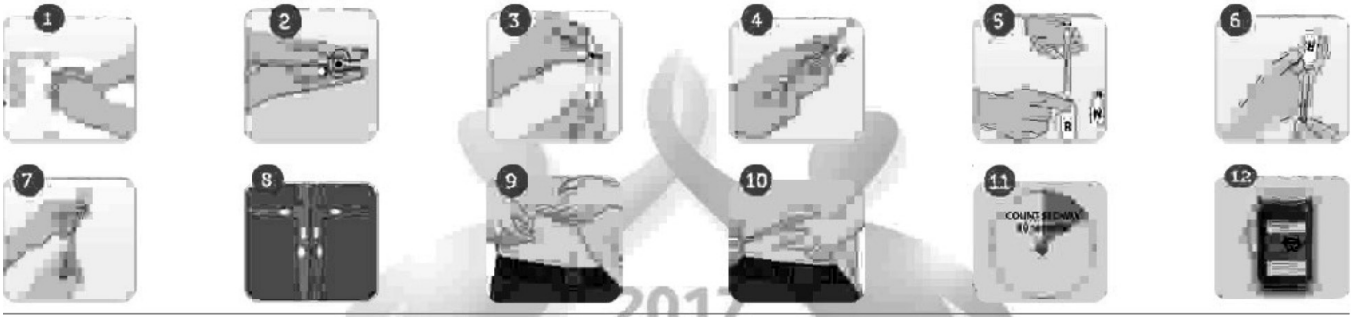

Fig 6a: Steps of injection technique using insulin syringe

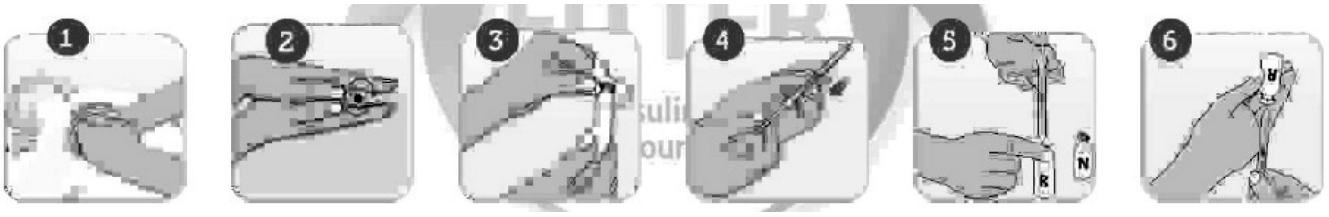

Fig 6b: Mixing insulin steps

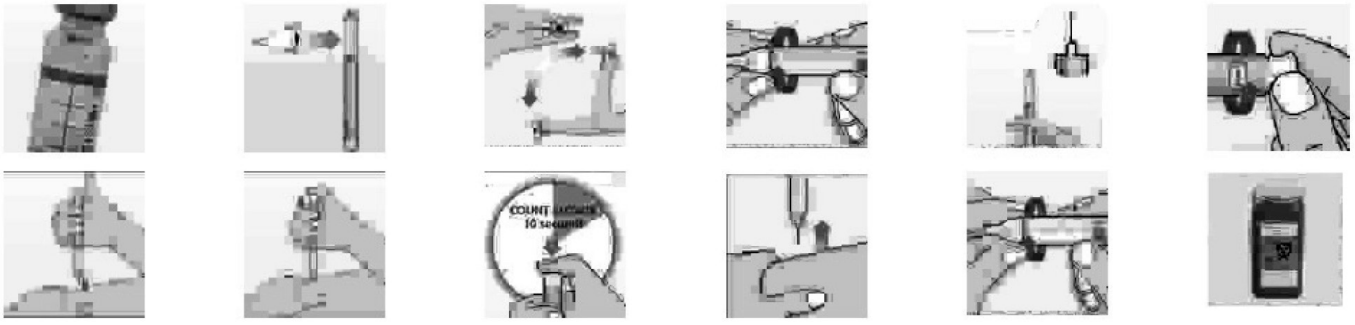

Fig 6c: Pen device preparation and injecting with the pen device

Table 16: Steps of injection technique

Step	Insulin syringe and vial	Mixing of insulins	Insulin pen
1.	Wash your hands	Wash your hands	Wash your hands
2.	Check expiry date and type of Insulin	Check expiry date and type of Insulin	Check expiry date and type of Insulin
3.	Bring insulin to room temperature	Bring insulin to room temperature	Bring insulin to room temperature
4.	For cloudy insulin, roll the bottle between your hands until it is uniformly cloudy	Draw air into the syringe equal to the dose of cloudy insulin desired	Ensure there is sufficient insulin for dose
5.	Wipe the top of the insulin bottle with an alcohol swab	Insert needle and inject air into cloudy insulin vial.	Re-suspend insulin if required
6.	Draw air into the syringe equal to the dose of insulin you wish to take	Remove the needle without drawing up the cloudy insulin.	Attach new needle
7.	Pierce the rubber stopper of the insulin vial in the middle at a 90° angle and push the air in.	Pull the plunger back to the dose of regular insulin desired; inject the air into the clear insulin vial	Prime the device observing drop of insulin at needle tip
8.	Holding the bottle upside down, draw the dose into the syringe. If air bubble present, it should be removed by drawing up several more units of insulin and re-injecting the bubbles into the vial	Hold the vial upside down and slowly draw the desired dose of regular insulin. Remove air bubble, if present and then needle from the vial.	Dial desired dose
9.	Ready for injection. Place the syringe on the table carefully without letting the needle touch the surface.	Holding the cloudy insulin vial upside down, and pull the plunger back to the marking that indicates the total dose of insulin.	Choose the appropriate site
10.	Select the site.	The mixed insulin is now ready to be injected.	Push the needle through the skin at 90° keeping thumb away from dosage button
11.	Clean the injection site with alcohol swab and it should be completely dry before you inject to avoid pain.	Select the site.	Push thumb button down completely and count to 10 or follow manufacturers recommendations
12.	To inject insulin, slowly push the needle through the skin fold.	Clean the injection site with alcohol swab and it should be completely dry before you inject to avoid pain.	Remove needle from subcutaneous tissue

13.	Count to 10 (more in case of large dose) before pulling the needle out. Release the skin fold and press an alcohol swab over the injected spot.	To inject insulin, slowly push the needle through the skin fold.	Remove needle from the pen
14.	Clip off the syringe needle with safe clip. Dispose off needle safely.	Count to 10 (more in case of large dose) before pulling the needle out. Release the skin fold and press an alcohol swab over the injected spot.	Dispose off needle safely
15.		Clip off the syringe needle with safe clip. Dispose off needle safely.	

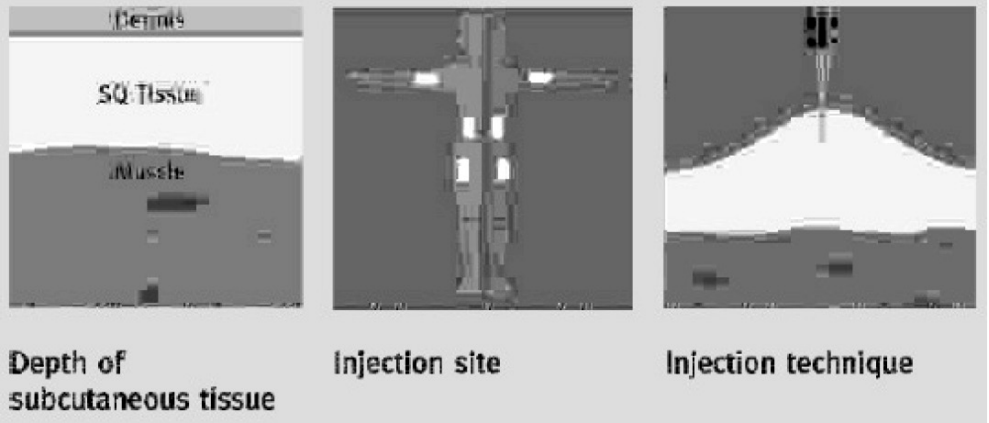

Fig 7: Factors for appropriate insulin injection.

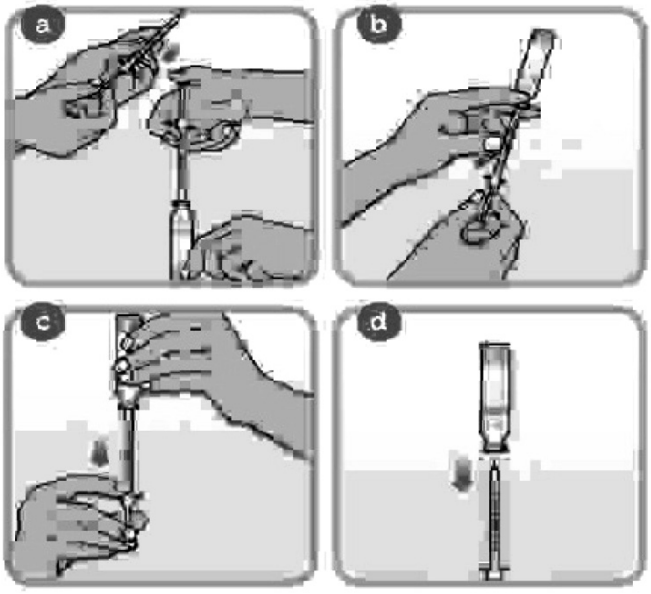

Fig 8: Using a syringe: One insulin, one vial.

12.5 Single use of insulin syringe/pen needle

The United States FDA recommends injection needles for single use only. On the contrary, in India, patients often reuse syringes and pen needles for several reasons including cost. Recent ITQ survey showed that 39.7% of insulin pen user reused needles 3-5 times or more and 44% syringe users reused needles an average of 3-5 times.

Blanco and coworkers demonstrated a clear correlation between the increased incidence of LH and needle reuse. Findings from a recent meta-analysis suggested an association between the presence of LH and reuse of needles. Also reuse of needles causes more pain at the injection site. 79% patient's reported not having received any guidance from HCPs, regarding single-use of needles and syringes.

12.5.1 Disadvantages of reuse of needles

- Distorted and bent needle results in more painful injection during reusing.
- Needle cleansing with alcohol prior to use removes the silicone lubricant and results in painful injection with reuse.
- Breaking off and lodging of the needles can occur under the skin.
- Reuse results in damage to the tissues and levies an increased risk of LH.
- Reuse of needles increases the risk of contamination and infection.
- Reuse of needles may leads to NSI among HCPs in hospital settings.

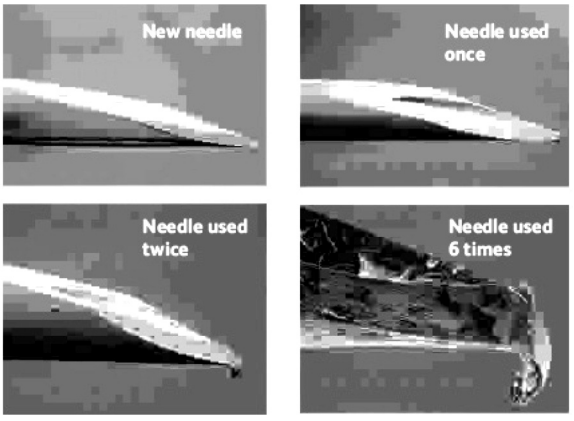

Fig 9: Needle reuse damages the tip of the needle

12.5.2 Impact to patients

75% of PWD reported reuse of disposable syringes and needles in a cross-sectional study (n=28). The prevalence of NSI, LH and hematoma due to syringes and needles reuse was 46%, 7% and 18% among PWD. Main reasons for syringe and needle changes were pain (54%), guidance of a health professional (14%) and blunt 108 needle (14%). Blanco et al. reported an association between LH and there use of needles with significant increase in risk when needles were reused more than five times. Among PWD, who reused needles, 70% reported LH while 61% patients with LH reported needle reuse as a main cause. HCPs should identify and educate PWD who are likely to reuse needles.

12.5.3 Impact to HCPs

A cross-sectional observational study from Gujarat, India conducted in government institutes assessed injection practices and prevalence of NSI among the HCPs. Out of 161 (64.14%) who were practicing unsafe injection methods, 65% had NSI ($P < 0.05$). Thus, proper training and infection control measures among HCPs can handle this future threat.

A systematic review of economic analyses involving 14 studies related to NSI found significant direct, indirect, potential, and intangible costs borne by the hospital, efforts directed at preventing NSI may help to lower these costs.

12.5.4 Recommendations

- Use a sterile, new needle for each injection (A2).
- Reuse increases the risk of LH (A2).
- HCPs should provide adequate guidance to PWD, 108 who are likely to reuse syringes and needles (A2).
- Patient information leaflet with advising statement against the reuse of syringe, pen needle and lancet boxes should be included in packs (B3).
- Photos from microscopy studies should be included in PIL and/or package inserts for patients and HCPs (B3).

- HCPs should be aware of reuse practices, in case the PWD makes an informed choice to reuse needles (B3).

Table 17: Needle/Syringe Hygiene

Needle reuse causes the blunting and bending of the needle tip, increasing the risk of: • Bleeding, bruising or scarring • Dosage inaccuracy • LH • HCPs should create awareness in patients regarding the potential adverse effects of needle reuse, and discourage this practice (A2).

12.6 Missing injections

All patients should be counselled about the negative effects of missing injections (A2). If a patient is admitted in the hospital and there is uncertainty about his current insulin regimen, rapid or short acting human insulin should be administered until further information is available. This should always be done under medical supervision.

Table 18: Missing injections: Recommendations

• Patients should be made aware of the consequences of missing injections (A2). • If there is a change in the insulin, then the patient should be fully informed as to why there has been a change and the potential need for additional glucose monitoring (A3). • Insulin species, type or brand name should not be changed unless absolutely indicated (A2).

12.7 Factors affecting rate of insulin absorption

The order of the rates of absorption at the sites is abdomen >arm >thigh >buttock . Factors which can speed up the absorption and cause hypoglycemia are hot environment, e.g. having a hot bath after the injection, which increases blood flow to the injection area, massage or exercise and IM injection of insulin.

Factors which can slow down absorption and cause a rise in blood glucose levels are large volumes of insulin, injections into damaged, unhealthy tissue, and cold environments (as they reduce blood flow).

12.8 "NO" Injection through clothing

This is a common practice among patients, especially when in a hurry, or in a public place. This practice should, however, be firmly discouraged (A3).

Table 19: Tips to prevent injection through clothing

• Injecting through clothing is not recommended (A3). • Injection practices are to be reviewed and addressed regularly (A3).

Table 20: Seven-step injection site care process

• Prior to injection, the site has to be inspected and palpated for LH and inspected for wounds, bruises or blisters (A3). • If the injection site shows any signs of LH, inflammation, edema or infection, a different site should be selected (A2). • Injection should be given at a clean site with clean hands (A2). • If the injection site is found unclean, it should be cleansed prior to injection (A3). • The injection site has to be inspected at every visit or atleast every 6 months, or as part of investigation into suboptimal or erratic blood glucose control (A2). • Rotate injection sites systematically (A2). • Ideally do not reuse needles (A2).

For further reference:

Visit fit4diabetes.com/india/recommendations

Part II of this article will be Published in next Issue of this Journal.

QUESTION AND ANSWERS

Q) What are the infections that one sees in diabetes?

A) Diabetes may slow down your body's ability to fight infections. Diabetes mellitus increases susceptibility to various types of infection. The most common sites of infection are the skin, kidneys, bladder, vagina, gums and feet. The high levels of sugars in the blood and tissues help infections develop by allowing the bacteria to grow.

Most of the infections in patients with diabetes can be treated if the patient is able to spot the symptoms like fever over 101 degree F, sweating or chills, skin rash, pain, tenderness, redness or swelling , wounds that don't heel, sore throat, pain while swallowing , nasal congestion, headache, white patches in mouth or on tongue, vaginal itching, bloody, cloudy or foul smelling urine.

Ear, nose and throat infection:

In patients with diabetes, malignant otitis externa and rhino cerebral mucormycosis are two head and neck infections. Malignant otitis externa is caused by Pseudomonas aeurginosa and occurs in patients older than 35 years of age. Patients suffer from severe ear pain and otorrhea. Whereas rhinocerebral mucormycosis is caused by ubiquitous molds. This occurs in patients with poorly controlled sugars especially in those with diabetic ketoacidosis.

Urinary tract infection:

UTI can be caused due to poor metabolic control, resistant pathogens, immune system impairments, bladder not fully emptying, fungal UTI, use of catheters, hospitalization, glycosuria. Patients with diabetes have an increased risk of asymptomatic bacteriuria and pyuria, cystitis, and more important, serious upper urinary tract infection. Pyelonephritis causes insulin resistance making diabetes control difficult. In addition, nausea may pose a problem in maintaining normal hydration. Treatment includes antibiotics and proper follow up till the infection is cleared.

Skin and soft tissue infection:

Atherosclerotic vascular disease, hyperglycemia, sensory neuropathy can lead to skin and soft tissue infection in patients with diabetes and this involves mainly the feet.

Foot infections:

Lack of blood supply from microvascular disease in association with lack of sensation, because of neuropathy in patients with diabetes mellitus leads to foot infection.

Signs and symptoms.

Diabetic foot infections take one of the forms from the following:

1) Cellulites:

   There is a presence of tender, erythematous, skin lesions, sometimes in addition with lymphangitis. Lymphangitis represents group A streptococcal infection. No ulcer or wound exudates are present.

2) Deep skin and soft tissue infection:

   There is extreme pain and tenderness that may indicate compartment syndrome or clostridial infection (i.e. gas gangrene, discharge if present is foul smell.

3) Acute osteomyelitis:

   Patient has pain at the site of involved bone.

4) Chronic osteomyelitis:

   Deep penetrating ulcers and deep sinus tracts are located between the toes or on the surface of the foot.

Management:

1) Cellulites: Responsive to antibiotics.
2) Deep skin and soft tissue infections: It is usually curable but additional debridement is indicated.
3) Acute osteomyelitis- Antimicrobial therapy.
4) Chronic osteomyelitis: Surgical intervention is essential in addition to antibiotics, amputation may be necessary.

Lung infection:

Patients, especially with type 1 diabetes, have a hard time dealing with infections of any type because of weak immune system.

1) Pneumonia: Caused by bacterial infection. A combination of rest and antibiotics is useful in treating pneumonia.
2) Tuberculosis: It is caused by bacterial infection .Treatment include long course of antibiotics usually about 6-9 months.
3) COPD: It is caused by swelling, inflammation and scarring of lungs. Treatment is to quit smoking and take medications to relieve symptoms.

DIVYA JAIN

Q) What is Hypoglycemia?

A) Hypoglycemia is diagnosed when blood glucose levels falls below 72 mg/dl. Early signs of hypoglycemia will allow to treat the low blood glucose levels quickly in order to bring them back to the normal level. The brain uses a lot of energy and needs glucose to function. Brain cannot store or manufacture glucose and thereby needs a continuous supply.

Symptoms:-

1. Sweating, Fatigue, Feeling dizzy, looking pale, Feeling weak, Feeling Hungry, Higher heart rate than usual, Blurred vision, Confusion, Convulsions, loss of consciousness, in extreme cases coma

Risks of patients of hypoglycemia

Low sugar can happen to anyone.

1. Insulin 2. Sulphonylureas 3. Prandial glucose regulators

Causes of Hypoglycemia

1. High dose of medication
2. Delayed meals
3. Exercise
4. Alcohol

Diagnosis of Hypoglycemia

Glucometer is the best way of diagnosing hypoglycemia. Any blood glucose levels below 72 mg/dl indicate that the individual has hypoglycemia. Hypoglycemia is not detected by the urine tests or by doing HbA1c. Also proper medical history is required about compliance in taking the medications or excessive exercise or skipping a meal. History is important in eliciting history of any recent bouts of heavy drinking.

Prevention of Hypoglycemia

1. **Checking blood glucose levels-** this involves keeping a regular check on blood sugar levels and knowing how to identify the onset of hypoglycemia.
2. **Eating regularly-** Eating at regular interval of 3 hrs.
3. Alcohol - A heavy drinking session can trigger hypoglycemia, individuals with Type 1 diabetes should stick to the alcohol limits.
4. Be ready- children with Type 1 diabetes should always carry a container of sugary fruit juice or a candy bar.

5. Awareness- If the individual is susceptible to the attacks of hypoglycemia, friends, colleagues and family members should be made aware.

DRASHTI KAMDAR

WHATS COOKING?

BROCCOLI SOUP

Ingredients :

INGREDIENTS	AMOUNT
Broccoli	150gm
Garlic	3-4 cloves (medium)
Onion	1 small
Milk	100ml
Corn flour	½ tsp
Salt-	to taste
Black pepper powder	1/4tsp

Method of preparation:

1. 1) Wash the broccoli properly and then chop it. Also include small portions of the stems.
2) Also chop the onions and garlic into bigger pieces.
3) In a bowl boil 250 ml of water; boil the broccoli, onions and garlic together.
4) After the stems are done, remove from heat and let it cool.
5) Grind it properly once it is cooled.
6) Add ½ tsp of corn flour to 100ml milk and mix properly.
7) Then boil the soup and then add the milk mixture and boil for 3-4 minutes on low flame.
8) Add salt and black pepper powder and serve.

Serves: 1

Nutritive value for 1 serving

Energy (kcals)	Carbohydrates (gm)	Protein (gm)	Fats (gm)	GI
80	13 gms	5gms	0g	Low

SOYABEAN VEGETABLE

Ingredients	AMOUNT
Soybeans	1/4th cup
Oil	2 tsp
Onion	1 small(chopped)
Tomato	½ medium (chopped)
Green chilly	1
Hing	1 pinch
Mustard seeds	¼ tsp
Jeera	1//4 tsp
Garlic	4-5 cloves (chopped)
Red chili powder	½ tsp
Coriander powder	½ tsp
Turmeric	¼ tsp

Method of preparation:

1) Soak soyabeans overnight in half cup of water. Cook in pressure cooker on low flame for 2 whistles.
2) Heat oil in a kadhai, add hing, then mustard seeds and jeera, after few seconds add chopped green chili and garlic, when the garlic turns slightly brownish add onions and sauté for a few minutes.
3) Once onions turn translucent, add chopped tomato and cook till soft, add all the masalas, then add ½ cup of water and let it come to boil.
4) Then add the cooked soybeans, mix properly and cover the kadhai with a lid. And cook for another 5 minutes. Add chopped coriander and serve.

Serves: 1

Nutritive value for 1 serving

Energy (kcals)	Carbohydrates (gm)	Protein (gm)	Fats (gm)	GI
170	17 gms	7gms	10g	Low

MULTIPLE CHOICE QUESTIONS

1) Acanthosis Nigricans is associated with:
   - Insulin Deficiency
   - Insulin Resistance
   - Hyperglycemia
   - Dyslipidemia

2) Fetal malformations in uncontrolled, pregnant diabetics are usually:
   - Hare lip and cleft palate
   - Osteogenesis imperfecta
   - Sacral regression
   - Hepato renal cysts

3) During active labour, a diabetic is likely to have:
   - Severe hyperglycemia
   - Drowsiness
   - Hypoglycemia
   - Severe labor pain

4) Which of the following nutrient is rich in short and medium chain fatty acids?
   - milk
   - peanut oil
   - sunflower oil
   - almond oil

5) Excessive thirst and volume of very dilute urine may be symptoms of
   - urinary tract infection
   - diabetes insipidus
   - viral gastroenteritis
   - hypoglycemia

6) The main cause of a low HDL cholesterol concentration in type 2 diabetes is
   - increased catabolism of HDL particles
   - low lipoprotein lipase activity
   - increased production of VLDL
   - visceral adiposity

7) Diabetic gastro paresis is caused due to
   - bacterial infection
   - slowing down of stomach emptying
   - excess eating
   - autonomic neuropathy of the gut.

8) Erectile dysfunction male diabetics is caused by
   - Diabetic nephropathy
   - Diabetic neuropathy
   - Diabetic cardio myopathy
   - Diabetic retinopathy

9) Clinical feature most likely to co-relate with insulin resistance
   - abdominal girth
   - body weight
   - hypertension
   - pedal edema

10) What is the most effective test to diagnose diabetes?
   - fasting glucose blood test
   - non fasting glucose blood test
   - vision test
   - urine test

ANSWERS:

1) Insulin Resistance: Insulin resistance and hyperinsulinemia causes proliferation of skin layers thus producing multiple skin folds and the typical appearance.
2) Sacral regression: It is a congenital disorder in which there is abnormal development of the lower spine. In the fetus it affects the caudal partition of the spine.
3) Hypoglycemia: The hepatic glucose supply is sufficient during the latent phase of labor but during the active phase of labor the hepatic glucose supply is depleted because of intensive uterine muscular activity. Hence

caloric supplementation is required, which is in the form of intravenous glucose

4) Milk: Milk fat contains approximately 400 different fatty acids which make it the most complex of all natural fats. Almost 70% of the fat in milk is saturated of which 11% comprises of short chain fatty acids almost half of which is butyric acid. Approximately 25% of fatty acids in milk are mono unsaturated and 2.3% are polyunsaturated with omega 6 to omega 3 ratio around 2.3. Approximately 2.7% are trans fatty acids.

5) Diabetes insipidus: People with diabetes insipidus produce excessive amounts of urine (polyuria) resulting in frequent urination and in turn thirst (polydipsia). Diabetes insipidus is caused by low or absent secretion of water hormone vasopressin from the pituitary gland of the brain or by a poor kidney response to this chemical messenger which is antidiuretic hormone.

6) Increased production of VLDL: Reduction of the hyperglycemia by means of dietary or pharmacologic interventions is associated with normalization of the rates of synthesis and catabolism of VLDL and their triglycerides. Thereby leading to atherogenecity due to VLDL production.

7) Autonomic neuropathy of the gut: The vagus nerve is damaged or stops working, the muscle of the stomach and intestines do not work normally and the movement of food is slowed or stopped. Diabetes can damage vagus nerve if blood glucose levels remain high over a long period of time. High blood glucose causes chemical changes in nerves and damages the blood vessels that carry oxygen and nutrients to the nerves.

8) Diabetic neuropathy- The cause of erectile dysfunction in men with diabetes is complex and involves impairments in nerves, blood vessels and muscle function. Diabetes damages the blood vessels and nerves that control erection.

9) Abdominal girth- Visceral obesity is closely linked to insulin resistance, and is a principal component of the metabolic syndrome. Insulin resistance is predictive of the risk of type 2 diabetes and cardiovascular disease. The optimal cut-off for predicting insulin resistance is more than equal to 90cm for men and more than and equal to 80cm for women.

10) Fasting glucose blood test- The fasting glucose blood test measures blood glucose levels after an overnight fast (no food intake for at least eight hours), Therefore, it is the most reliable test.

MEMBERSHIP FORM

Association of Diabetes Educators (ADE)

(For eligibility criteria: Check Website www.diabeteseducatorsindia.com)

Name ……..……..

Address ……..……

……

Telephone: Res: ….....…… Office: ……..... Cell: ……

E-mail id: ….....……..

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Work Experience: ….....……

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Currently employed at: ……

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Certificates attached regarding educational qualification and work experience:

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₹ 1000/- is payable in cash / cheque / draft with the application form

Add ₹ 100/- for outstation cheques

Cheque Drawn in favour of: Association of Diabetes Education

Payment Details: Cheque No./Draft No. _____ Dated _____

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BOOK REVIEW

RSSDI text book of Diabetes Mellitus; Editor-in-Chief: H B Chandalia, Executive Editor: G R Sridhar, Editors: A K Das, S V Madhu, V Mohan, P V Rao

Jaypee Brothers Medical Publishers; New Delhi; 2014; pages 1457; Price Rs 2995

The third edition of RSSDI Text Book of Diabetes Mellitus (D M) has been published six years after the second edition. It is authored and edited by those clinicians and professors who have been teaching and practising diabetes over many years within the country. A few chapters are contributed by Non-resident Indians. As pointed out by the editor-in-chief, this edition has undergone considerable revision. The material published both within the country and outside till the end of 2013 has been critically analysed and included. A few topics which are paid scant attention in other books, like-the complexity of insulin resistance, the criteria applicable to metabolic syndrome in Asians,challenges in the management of children and elderly with diabetes,musculoskeletal manifestation of diabetes, malnutrition modulated diabetes, Latent Autoimmune Diabetes in Adults (LADA), neonatal diabetes and the role of Yoga and relaxation techniques are unique to this book.

The flow chart on the management of diabetic ketoacidosis available in this book should be in possession of all ICUs. The colour pictures of retinopathy, foot lesions, skin diseases and musculoskeletal manifestation are well presented. The role of alternate therapy is extensively discussed. The guidelines for the beginner to organise a diabetic clinic and optimal health care for diabetes amidst diversity of social, economic and regional food habits is noteworthy. The limitation of stem cell therapy as of now is a good reminder. Some controversial issues are discussed in individual chapters. Much alike the chapter on A Glimpse in the Future, I wish a full chapter was devoted to controversies in diabetes. New chapters added in this edition are valuable and discuss important current issues. These include Sleep and Type 2 diabetes-mellitus, Early-onset Type 2 DM, Nutrient blockers and Bromocriptine, Insulin Pump Therapy, Glycemic Management in Hospitalized Patients, Continuous Glucose Monitoring System, Vitamin D and DM, HIV in Diabetes, Diabetes and Cancer.

The appendix is retained from the previous edition and gives a wealth of information applicable to Indian subjects like BMI and waist circumference and laboratory values in S I and conventional units.The index has attained perfection.The novel feature of this edition is mentioning the chapter number on the right edge of each page.

The book will prove to be valuable to students, physicians, diabetologists, endocrinologists and providers of diabetes care. It should be on the shelf of every medical library. The availability of this book has made the Western text books redundant. The single volume covering so many topics is bulky and heavy. I wish it was brought out in two volumes.

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Prof (Dr) H B Chandalia's creative writing abilities & practical acumen has always been illustrated by his multiple contributions as an author of chapters in various textbooks. One such outstanding example is the book **'Conquest of Diabetes- by diet & exercise'** which is running its fourth edition in the English language and also available in Hindi as well as Gujarati. The Marathi version of the book is under preparation. It is a comprehensive, extensively illustrated two color book which is characterized by its brevity, clarity and offers a systematic approach towards the management of diabetes by diet and exercise.

The book highlights very important issues and controversies in the form of a large number of box inserts. Also, the scientific and technical words have been explained in the glossary, which appears throughout the book.

It also deals with recipes and an exercise plan for diabetics, which would prove helpful.

This book is directed to persons suffering from diabetes, health-care practitioners like doctors, nutritionists and diabetes educators and other health professionals involved in the care of diabetics.

Available at:

Dr. H.B. Chandalia's

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ABRIDGED PRESCRIBING INFORMATION:

PRODUCT DESCRIPTION: Trulicity (dulaglutide) 0.75 mg/1.5 mg solution for injection in pre filled pen. **INDICATIONS AND USAGE:** Trulicity is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as Monotherapy (The recommended dose is 0.75 mg once weekly) and Add-on therapy (The recommended dose is 1.5 mg once weekly). In monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Add-on therapy- In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **ADVERSE REACTIONS:** In the phase II and phase III studies conducted, 4,006 patients were exposed to Trulicity alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions in clinical trials were gastrointestinal, including nausea, vomiting and diarrhoea. In general these reactions were mild or moderate in severity and transient in nature. **USE IN SPECIFIC POPULATIONS:** For pregnancy, there are no or limited amount of data from the use of Trulicity in pregnant women. Studies in animals have shown reproductive toxicity. Therefore, the use of Trulicity is not recommended during pregnancy. For Breast feeding, it is unknown whether Trulicity is excreted in human milk. A risk to newborns/infants cannot be excluded. Trulicity should not be used during breast-feeding. The effect of Trulicity on fertility in humans is unknown. In the rat, there was no direct effect on mating or fertility following treatment with Trulicity.

HUMALOG® 200 units/mL U-200 Abbreviated Prescribing Information

HUMALOG 200 units/mL U-200 is available as: • 3 mL Humalog KwikPen® (prefilled). **INDICATIONS AND USAGE:** HUMALOG 200 units/mL is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. **ROUTE OF ADMINISTRATION:** Subcutaneous Injection: HUMALOG U-100 or U-200. Administer the dose of HUMALOG U-100 or HUMALOG U-200 within fifteen minutes before a meal or immediately after a meal by injection into the subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks. **DOSAGE INFORMATION:** Individualize and adjust the dosage of HUMALOG based on route of administration, the individual's metabolic needs, blood glucose monitoring results and glycemic control goal. Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness . Do NOT transfer HUMALOG U-200 from the KwikPen to a syringe for administration. Do NOT perform dose conversion when using either the HUMALOG U-100 or U-200 KwikPens. The dose window shows the number of insulin units to be delivered and no conversion is needed. Do NOT mix HUMALOG U-200 with any other insulins. Do NOT administer HUMALOG U-200 using a continuous subcutaneous infusion pump (i.e., insulin pump). Do NOT administer HUMALOG U200 intravenously. **DOSAGE FORMS AND STRENGTHS:** HUMALOG 200 units per mL (U-200) is available as: • 3 mL Humalog KwikPen (prefilled) **CONTRAINDICATIONS:** HUMALOG is contraindicated: • During episodes of hypoglycemia. • In patients who are hypersensitive to HUMALOG or to any of its excipients **UNDERSIRABLE EFFECTS/ADVERSE EVENTS:** Hypoglycemia is the most common adverse reaction associated with insulins, including HUMALOG. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypokalemia All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death.

Consult the package insert for complete prescribing information.

Humalog® (Insulin Lispro I.P.), Humalog Mix25® Insulin Lispro Biphasic Injection I.P. (25% Insulin lispro and 75% insulin lispro protamine suspension) (100 IU/mL, 3 mL Cartridge) and Humalog® Mix50 Insulin Lispro Biphasic Injection I.P. (50% Insulin Lispro and 50% insulin Lispro protamine suspension) (100 IU/mL, 3 mL Cartridge) **INDICATIONS AND USAGE:** Humalog® is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. **CONTRAINDICATIONS:** Humalog® is contraindicated during episodes of hypoglycemia. It is also contraindicated in patients with hypersensitivity to insulin lispro or any of the excipients contained in the formulation. **ADVERSE REACTIONS:** Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise. Local allergy in patients is common (1/100 to <1/10). Redness, swelling and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. **USE IN SPECIFIC POPULATIONS:** Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin Lispro on pregnancy or on the health of the foetus/newborn. It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Renal and hepatic Impairment: Insulin requirements may be reduced in the presence of renal impairment.

HLG/Cycle Feb 2017/06

Talk about it

† IT = Injection Technique

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References:

1 Pen needle clinical study, conducted by Bruno and Ridgway among 143 diabetes patients, December2009.

2. Hirsch LJ, et al. Curr Med Res Opin 2010; 6: 1531-41. 3. Gibney MA, et al. Curr Med Res Opin 2010;26(6):1519-30.

* As at June 2017. #Patients aged 2–6 or extremely lean adults may require a pinch-up.

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Becton Dickinson India Private Limited
5th & 6th Floor, Signature Tower -B, South City - 1, Gurugram-122001
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