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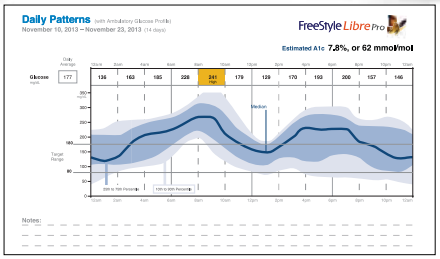

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MINIMIZING HYPOGLYCEMIA WITH INSULIN THERAPY

*Hemraj. B. Chandalia**

Introduction:

Basic effect of insulin is to lower blood glucose. Hypoglycemia can be visualized as an extension of the same effect and hence an inevitable consequence of insulin therapy. Hypoglycemia is a formidable barrier to achieving optimal control of diabetes. Hence a strategy to minimize hypoglycemia in insulin therapy is extremely important for a successful outcome. This chapter describes the incidence of hypoglycemia with insulin therapy and the complications caused by hypoglycemic episodes. It further describes means to optimize insulin therapy by adhering to insulin regimes that closely mimic normal physiology. It further recommends insulin regimes incorporating adequate amounts of basal insulin and the use of insulins with lower intra-subject coefficient of variation of insulin response. It further describes use of insulin sensitizers in T2DM, in order to lower the dosage of insulin required. It describes situations where an upward revision of glycemic targets is justified. A cautious approach has been advocated in elderly subjects on insulin therapy and in those experiencing nocturnal hypoglycemia and hypoglycemia unawareness.

Incidence of Hypoglycemia with Insulin Therapy:

In UKPDS the incidence of major hypoglycemic episodes has been reported to be 0.6% per year in the sulfonylurea-treated group and 2.3% per year in the insulin-treated group (1). The incidence was higher in the intensive treatment arm as compared to the standard treatment arm. In DCCT study the incidence of hypoglycemia per year was 10% in the conventional treatment arm and 30% in the intensive treatment arm. Thus the incidence is trebled in the intensively treated patients as compared to conventionally treated group (DCCT) (2). In the ADVANCE (3) ACCORD (4) and VADT (5) studies the incidence of hypoglycemia was very high in the intensively treated group. (Standard group per year respectively 1.1 %, 0.4%, 4.0%, intensive group per year respectively 3.1%, 0.7% and 12%) The magnitude of weight gain with insulin therapy is also proportionally increased in those on intensive therapy and in whom hypoglycemia was more frequent or severe (2). The weight gain was average 2.2 kg; intensive treatment arm 4.6 kg and in those experiencing hypoglycemia 6.8 kg. Although weight gain of an average of 3-5 kg has been ascribed to insulin therapy, this probably occurs in those subjects who had lost weight prior to the institution of effective treatment (6). We also need to differentiate between mild and severe hypoglycemia. The latter requires external assistance, and may even need hospitalization in order to reverse the hypoglycemia.

Complications due to hypoglycemia:

The immediate dangers of hypoglycemia are very well recognized. However, some additional dangers of hypoglycemia are now being described.

Recurrent severe hypoglycemia can impair cognitive function (7). In fact, recurrent episodes of severe hypoglycemia raise the hazard ratio for cognitive impairment considerably (1 episode: HR 1.26; 2 episode: HR 1.8; 3 episodes: HR 1.9). Recurrent hypoglycemia has been documented to increase cardiovascular disease (8).

Hypoglycemia can induce a sudden autonomic failure, so called, Hypoglycemia Associated Autonomic Failure (HAAF) (9). This is acute and transitory and bears no relationship to preexisting autonomic neuropathy. It can prevent mounting of cardiovascular responses to maintain blood pressure in the face of hypotension and hence, its failure can be disastrous in a diabetic during surgery and anesthesia. In type 1 diabetics, insulin-induced hypoglycemia has been shown to lower potassium and increase QTc interval, which is likely to produce cardiac arrhythmia (10). This may be responsible for a ‘dead in bed’ event, especially if seen in an undisturbed bed.

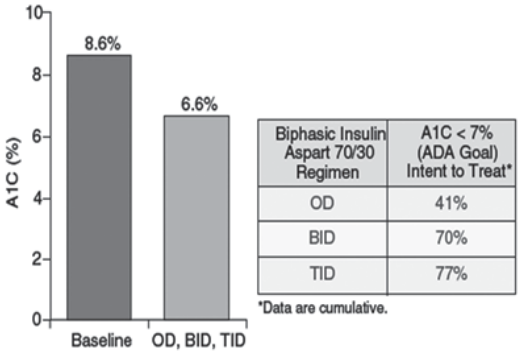
Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (4) showed a significantly increased cardiovascular mortality in intensively treated group. In this study, subjects with pre-existing cardiovascular disease were recruited. However, on further analysis, the increased cardiovascular deaths were not directly attributable to hypoglycemia in the intensively treated group. Further analysis showed that rapid lowering of blood glucose from the original very high levels could be injurious to

* Dr. H.B. Chandalia, Director, at Dr. Chandalia`s Diabetes Endocrine Nutrtion Management and Research Center (DENMARC) and Department of Endocrinlogy and Metabolism Jaslok Hospital • Email Id: denmarc100@gmail.com

the cardiovascular system. On the basis of these data, the current approach consists of rigid glycemic control in the initial period of 5-10 years after diagnosis, while a relaxed control in diabetes of duration longer then 10-20 years. It is heartening to note that the meticulous control of early years translates into greater cardiovascular benefits than similar metabolic control after 10-20 years of Type 2 DM (11). Furthermore, it is feasible to achieve tight glycemic control in the first decade of diabetes quite easily as compared to the latter period.

Optimized Insulin Therapy:

Optimization of insulin therapy can reduce the incidence of hypoglycemia. Several decades ago an interesting system called Glucose Controlled Insulin Infusion System (GCIIS) was used in critical-care settings and later on, for doing glucose or insulin clamp studies (12). These systems incorporated a glucose sensing system and algorithms to calculate the dose of insulin or intravenous glucose required and inject it through a triluminal catheter to maintain predefined target blood glucose. These devices produced insightful data regarding the physiological insulin requirement in a diabetic.



Biphasic Insulin Aspart 70/30 Regimen	A1C < 7% (ADA Goal) Intent to Treat*
OD	41%
BID	70%
TID	77%

*Data are cumulative.

Fig 1 : Better attainment of HbA1C targets with multiple insulin doses (Ref 13)

Notably, these devices showed that about half of the insulin requirement was for basal needs, mainly at night and during the inter-prandial periods. Other half of the requirement was meal-related, of which maximum dose required was pre breakfast, and minimum dose required was pre-lunch. The pre-dinner dose was usually intermediate between the two. The high pre-breakfast requirement was not related to breakfast size but was due to inherent blood glucose rhythm leading to a surge of morning hyperglycemia, probably related to choronobiology of growth hormone and cortisol. An appreciation of these facts enables a diabetologist to rationally plan near-physiological insulin dosing. In view of these data it is easy to appreciate that two or three injections of premixed insulins is a very poor strategy and is likely to work only in a limited number of patients. 1-2-3 study has shown that multiple doses of biphasic aspart 70/30 of insulin permits a higher proportion of patients to achieve HbA1c goals than a single or two premixed dose insulin regime (13) (Fig1). In ALL-TO- TARGET study, 2 doses of premix insulins, 1 dose each of glargine and glulisine and one dose of glargine plus 3 doses of glulisine were added to type 2 diabetics poorly controlled on 2-3 OAD's. The glargine plus 3 doses of glulisine achieved significantly better glycemic control (14).

Use of adequate dose of basal insulin

The incidence of hypoglycemia was shown to be maximum with the use of a prandial insulins (insulin aspart) and minimum, with the use of basal insulin (detemir). It was intermediate with the use of biphasic aspart insulin (15) (Table 1). Hence, optimizing the dose of basal insulin, which in turn is expected to lower the prandial insulin dose, will result in lower incidence of hypoglycemia. As expected, weight gain runs parallel to hypoglycemia. Therefore, it is maximum with prandial insulin as compared to basal.

Table 1:- Hypoglycemia and weight gain with biphasic, prandial or basal insulin in type 2 diabetes (Ref 15).

- N= 708, SU+MF, add Insulin for 1 yr.

Group		Results		
	A1c	A1c < 6.5 (N)	Hypoglycemia	Wt gain (kg)
Biphasic aspart	7.3	179	5.7	4.7
Prandial aspart	7.2	249	12.0	5.7
Basal (Detemir)	7.6	89	2.3	1.9

A review of a series of basal-bolus insulin doses used at our center has shown basal insulin dose to be 14.6 ± 6.7 % of total. The lower proportion of basal insulin appears to be a common error in insulin dosing, especially prevalent in India, while the doses in Western Countries have often erred on the other side. The basal insulin, especially insulin glargine was usually injected at the bed time, as it has a minor peak after 7-8 hours of injection, which could be coincided with the morning surge of blood glucose. However, presently patients experiencing nocturnal hypoglycemia are often receiving the glargine dose in the morning, around breakfast time. When glargine is injected at night the fasting blood glucose is targeted and dose is adjusted to "fix the fasting" blood glucose. However, all basal insulins also lower the prandial blood glucose as well and prandial insulins, more so the human regular than

the rapid acting analogues, have an interprandial basal effect. Hence, the slogan "Fix Fasting First" may not have complete validity. Once a reasonable control is achieved, fine tuning of insulin dosage can be done by using Continuous Glucose Monitoring Systems (CGMS).

Coefficient of Intra subject Variation of insulin response

One major cause of hypoglycemia with insulin therapy is a large intra-subject coefficient of variation of insulin response. This fact has been known for long time but has been emphasized only for the past 2 decades with the advent of newer insulins. (Table 2) (16)

Table 2:- Intra-individual Coefficient of Variation of Insulin Response (Ref 16)

	Approximately
Regular Insulin	20 %
NHP / Lente Insulin	30 - 40%
Biphasic Insulin	?
Lyspro, Aspart, Apidra	20 %
Glargine, Detemir	20 - 40%

The intra-subject coefficient of variation of insulin response with currently used insulins is about 15-40%. The variation is less with short or rapid acting insulins, as compared to basal insulins, the exception being ultra-long acting insulin like degludeg. Degludeg insulin has a half-life of about 24 hours which produces a very steady level of insulin after 2-3 days of dosing with a low intra-subject coefficient of variation of about 15 %. This results in much lower incidence of hypoglycemia; this is further evident with regards to nocturnal hypoglycemia which as compared to insulin glargine is reduced by 42 % in Type 2 DM and 36 % in Type 1DM (17, 18). In order to minimize the impact of variation in insulin response, it is important to use multiple small doses of prandial insulins. It is also important to use an insulin sensitizer, so that overall insulin dose is small. The method of delivery of insulin also is important; intravenous insulin giving a highly predictable response and hence, used in all critically ill subjects. Use of insulin pump reduces the variability to 3 % thus producing a consistently predictable response (19). In fact, the main reason why use of insulin pumps is associated with better glycemic control is reduced variability of insulin response with the pump. Newer analogues are attributed with lower variability of response, but data in this regard are at variance and need to be established by independent studies. Rotation of insulin injection site appears to be a simple precaution, but extremely important. Lipohypertropy is described in 49 % insulin users and may be responsible, in part, for the variation in insulin response (20)

Use of Insulin sensitizer in Type 2 DM

Most diabetologists treat Type 2 DM of long duration with optimized insulin therapy along with an insulin sensitizer. Metformin and pioglitazones are pre-eminent examples of sensitizers in use. However, it is important to appreciate that many other classes of oral anti-diabetic agents also work as are insulin sensitizers, or at least their use is attended by a reduction of insulin dosage. This holds true of sulfonylureas, DPP 4 inhibitors, SGLT-2 blockers and alpha glucosidase inhibitors. Sulfonylureas were the first class of drugs shown to possess insulin sensitizing activity. Their extra-pancreatic effects, like effect on insulin receptors, post receptor events and hepatic gluconeogenesis are well documented (21). Metformin is the most well accepted and widely used sensitizer, with clear effects on hepatic glucose production. It is the only drug which showed a reduction in cardiovascular death in Type 2 DM in UKPDS study (1). Only contraindications are hepatorenal disease and gastrointestinal intolerance. Pioglitazone is an excellent sensitizer and presently it has been exonerated from a potential of carcinogenesis. Hence its use can be expanded. It is contraindicated when side effects of excessive fluid retention are likely to produce clinical problems like heart failure or when excessive weight gain occurs in the first 2-3 months of therapy. It causes moderately severe loss of bone mineral density. Hence, it should be used cautiously in post-menopausal women.

Revision of glycemic Targets

A need for revision of glycemic targets based on the duration of diabetes was recognized by clinicians for a long time (22). However, it has been articulated conclusively only in the past decade. Need for revision of glycemic targets is based upon type of diabetes, duration of diabetes, incidence of hypoglycemia with optimized therapy, patient's age and life expectancy, patient education, availability of patient support systems and presence of complications (23,24). Furthermore, the same arguments have been advanced in various types of diabetes, associated with pregnancy. (Type 1 DM, pregestational Type 2 DM, gestational DM) (24). This recommendation is partly based on the incidence of hypoglycemia observed with optimized therapy in different types of diabetes in pregnancy.

The case for revision of glycemic targets was made more

forcefully with the availability of ACCORD data where patients with pre-existing vascular complications were put on Standard and Tight control treatment arms, the target HbA1c in intensive control being 6%. This resulted in increased cardiovascular mortality in the intensive group. This prompted most diabetologists of individualize glycemic targets.

DPP4 inhibitors and SGLT-2 blockers have been documented to reduce the insulin requirement by about 20%. (25,26). The lowering of insulin dose is a very important objective; not from the point of view of insulin economy but because of the fact that the reduction of insulin dosage renders each dose very small and thus minimizes the absolute amount of variation in each insulin dose. This results into diminished glycemic excursions and diminished hypoglycemia.

With the availability of new insulin sensitizers, it is advisable to avoid sulfonylureas, as this may aggravate hypoglycemic events. However, a small dose of unmodified gliclazide (20 mg TDS, premeal) may be a very effective sensitizer and does not produce significant hypoglycemia.

Hypoglycemia with insulin therapy : special situations

Elderly diabetics on insulin therapy.

Elderly diabetics are more prone to hypoglycemia because of one or several of the following factors: hepato-renal insufficiency, unpredictable food intake, poor cognitive function, inadequate support systems and drug interactions (27). They may also have hypoglycemia unawareness, whereby they go into neuroglycopenia without premonitory symptoms of sympathoadrenal discharge. Hence, insulin therapy in these patients should be undertaken extremely cautiously, observing all precautions discussed in this article.

Nocturnal hypoglycemia:

Nocturnal hypoglycemia produces considerable fear and anxiety on the part of diabetic patients, thus making optimisation of therapy difficult. There is possibility of Q-T Prolongation and arrhythmia induction with hypoglycemia which can be more dangerous in night sleep. It is also known that counter-regulatory mechanisms to hypoglycemia are delayed or blunted in sleep (28). Diabetics living alone have to assiduously avoid nocturnal hypoglycemia.

Some practical measures to tackle nocturnal hypoglycemia are: ingestion of a bed time snack, replacing human regular insulin at predinner time with a rapid acting analogue (29), and shifting bed time basal insulin to morning time.

Hypoglycemia unawareness:

In this situation, the patients suffer from a sudden episode of neuroglycopenia and mental obtundation without pre-monitory symptoms of sympathoadrenal discharge. It is usually seen in diabetics of long duration who have been on rigid glycemic control. In these situations, a relaxation of glycemic control for a period of 3 weeks will result into restoration of hypoglycemia awareness (30). However, a permanent resolution is only possible by revising the glycemic targets upwards.

Conclusions:

Hypoglycemia is an inevitable accompaniment of insulin therapy. Strategies to minimize hypoglycemia hold the key to successful insulin therapy.

The insulin therapy has to be planned to mimic physiological insulin requirement. As about 40-50% of insulin requirement is for basal needs, it is important to use basal insulin in this proportional dose. Basal insulin also has lower propensity to produce hypoglycemia than prandial insulins. For prandial glucose regulation, multiple small doses of prandial insulin are required to minimize hypoglycemia. Hence, a classic basal-bolus therapy is highly recommended. It produces a much lower incidence of hypoglycemia than a two dose mixed insulin therapy. The intra-subject coefficient of variation of insulin response is 20-40%; hence use of insulin with lower coefficient of variation is desirable. In this regard human regular or rapid acting insulin analogues and newer ultralong-acting basal insulins are preferred. Lowest coefficient of variation of insulin response is seen with the use of insulin pump, which is a very effective tool to reduce the incidence of hypoglycemia in Type 1 diabetics.

It is also important to use an insulin sensitizer in type 2 diabetic. This leads to reduction in the insulin dosage, which further attenuates the variability of insulin response, thus leading to reduced hypoglycemia. It is advisable to use an antidiabetic agent like metformin, DPP4 inhibitor, SGLT2 inhibitor or pioglitazone, which are least likely to cause hypoglycemia.

Special precautions need to be undertaken in patients exhibiting nocturnal hypoglycemia and hypoglycemia unawareness. In elderly subjects where the symptoms of sympathoadrenal discharge and neuroglycopenia are only separated by a narrow band of 10-15 mg blood glucose, insulin therapy should be undertaken very cautiously.

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BRANCHED CHAIN AMINO ACIDS

*Tejal Shah**

Branched chain amino acids are the essential amino acids, which are generally not synthesized in the body. These include Leucine, Isoleucine and Valine. Liver does not produce these amino acids, Hence it should be added in daily dietary intake.

SOURCES OF BCAA:

Animal sources:

Meat, Chicken, Fish, Eggs and Dairy products like Milk and Cottage cheese. Whey protein is also good option of boosting your intake of BCAAs.

Plant sources:

Soybeans, Black beans, Lima beans, Lentils, Brown rice, Whole wheat, Corn and Nuts such as Almonds and Cashews are good source of BCAAs.

Uses of BCAAs:

- Renal failure patients.
- Liver failure patients.
- Brain conditions due to liver disease.
- Cancer patients.
- To prevent fatigue and improve concentration.
- It is also used to help slow muscle wasting in people that are confined to bed.
- A movement disorder called Tardive Dyskinesia.
- Amyotrophic lateral Sclerosis.

Athletes use BCAA to improve exercise performance and reduce protein and muscle breakdown during intense exercise.

Benefits of BCAAs:

People who consume a threshold dose of essential amino acids that contains BCAAs with every meal have less visceral belly fat and more muscle mass.

BCAAs trigger protein synthesis and inhibit the breakdown of muscle cells.

In diabetics, dietary intake of BCAAs improves glucose uptake and insulin sensitivity.

BCAAs are often used during workouts, as it increases the muscle and energy production during exercise.

They also reduce muscle soreness from intense muscle damaging due to exercise.

BCAAs in Management of Renal failure

Kidneys are involved in many aspects of protein metabolism and amino acids synthesis. Patients with chronic renal failure or End stage renal disease treated by dialysis suffer from multiple disturbances of amino acid (AA) metabolism, including BCAAs. These disturbances of amino acids results in depletion of BCAAs and BCKA (branched -chain Keto acid), which alter tissue activities, particularly brain function and nutritional status.

In dialysis or chronic renal failure patients, oral supplementation of BCAA can induce an improvement in appetite and nutritional status. The aims at nutritional interventions are to minimize uremic toxicity, avoid malnutrition and delay progression of kidney disease.

BCAAs in Management of chronic Liver disease

Liver plays a central role in protein and amino acid metabolism. It helps in regulating the supply of amino acids to peripheral tissues and converts excess amino acids into urea. It also utilizes amino acids for protein synthesis and gluconeogenesis. In the patients with liver disease, the ability to control both plasma and tissue amino acids fluxes may be disturbed and amino acids are imbalanced, which worsen the prognosis of patients. Research shows that supplementation with BCAAs or BCAAs rich medicines reduces hepatocyte apoptosis and promots liver regeneration resulting in rapid recovery from liver injury. It is also reported that late evening snacks with BCAA were useful in improving protein metabolism and lipolysis in cirrhotic patients.

Metabolism of BCAAs in Brain

The branched-chain amino acids (BCAA) particularly leucine, plays an important role in the synthesis of brain glutamate, which is efficiently transported into the brain.

The uptake of leucine across the blood brain barrier is faster than any other amino acids. Leucine acts as an alternative to glucose. It also serves as a regulator of the activity of some enzymes important in brain energy metabolism.

* Tejal Shah, Nutritionist at Dr. Chandalia's Diabetes Endocrine Nutrition Management and Research Center (DENMARC), Mumbai.

SOURCES OF BRANCHED CHAIN AMINO ACIDS WITH ITS VALUE

FOOD SOURCE	SERVINGS	GRAMS	PROTEIN IN GRAMS	BCAAs IN GRAMS	LEUCINE	ISOLEUCINE	VALINE
CHICKEN BREAST	1	100	21.42	3.92	1.72	1.07	1.13
WILD SALMON	1	100	20.2	3.51	1.60	0.89	1.01
CANNED TUNA	1	100	19.64	3.33	1.48	089	0.95
TURKEY BREAST	1	100	23.8	3.09	1.66	0.65	0.77
NON FAT YOGURT	1BOWL	250	14	3.4	1.4	0.8	1.2
SKIM MILK	1 CUP	200ML	9.7	2.3	1.0	0.6	0.7
SOY BEANS	1 OZ	30	10.92	2.18	0.99	0.59	0.60
WHOLE MILK	1 CUP	200ML	7.7	1.6	0.7	0.4	0.5
EGG WHITE	2		7.2	1.6	0.6	0.4	0.6
CHEDDAR CHEESE	1OZ	30	6.8	1.3	0.6	0.3	0.4
WHOLE EGG	1		6.3	1.3	0.54	0.3	0.4
ROASTED PEANUTS	1 OZ	30	2.14	1.21	0.55	0.30	0.35
BLACK BEANS	1 OZ	30	6.4	1.13	0.5	0.29	0.34
WHEAT GERM BREAD SLICE	2 SLICE		5.4	0.8	0.4	0.2	0.2
BROWN RICE	1 OZ	30	2.5	0.45	0.2	0.1	0.15
LENTILS	1 OZ	30	2.68	0.44	0.2	0.1	0.14
WHEY POWDER	1 SCOOP	25	15	2.78	1.29	0.72	0.77

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ROLE OF NUTS IN HEALTHY EATING

*Drashti Kamdar**

Nuts are nutrient dense foods with complex matrices rich in unsaturated fatty acids and other bioactive compounds-high quality vegetable protein, fiber, minerals, tocopherols, phytosterols and phenolic compounds. Nut consumption with a reduced incidence of coronary heart disease and gall stones in both genders and diabetes in women. Nuts also have an effect on hypertension, cancer and inflammation. Nut intake has cholesterol lowering effect also there are beneficial effects on oxidative stress, inflammation and vascular reactivity. Blood Pressure, visceral adiposity and the metabolic syndrome also appears to be positively influenced by nut consumption. Contrary to expectations, epidemiologic studies and clinical trials suggest that regular nut consumption is unlikely to contribute to obesity and may even help in weight loss. Nuts are nutrient rich foods with wide ranging cardiovascular and metabolic benefits, which can be readily incorporated in healthy diets. Thereby here are few Nuts mentioned which have their own properties and are thereby classified as follows:

Almonds: Almonds are revered as an epitome of wellness and health. The kernels are among the richest sources of health benefitting nutrients essential for optimum health.

Health Benefits:

1. Almonds are rich sources of vitamins, minerals and also many phyto chemicals. These nuts compose of well balanced food principals that are optimum for health and wellness.
2. Almonds are one of the complete sources of energy as well as nutrients.
3. Nuts are rich in MUFA like oleic and palmitoleic acids that help in lowering LDL or bad cholesterol and increasing HDL or good cholesterol in the human body. There are many research studies which state that Mediterrian diet is excellent in MUFA's and help prevent coronary artery disease and strokes by favoring healthy blood lipid profile.
4. Almonds are also excellent source of Vitamin E which holds upto 25 mg per 100gms. Vitamin E is a powerful lipid soluble antioxidant. It protects and restores cell membranes integrity of mucosa and skin from harmful effects of oxygen free radicals.
5. Almonds are gluten free food items. Therefore one of the favorite ingredients in the preparation of gluten free food formulas.
6. The nuts packed with B complex groups of vitamins such as riboflavin, niacin, thiamin, pantothenic acid, vitamin B6 and folates. Altogether these vitamins work as a cofactor for enzymes during cellular substrate metabolism inside the human body.
7. Furthermore almonds are also an incredible source of minerals such as manganese, potassium, calcium, iron, magnesium, zinc and selenium.
8. Almond oil, extracted from the nuts is a good source of emollient. When applied regularly it helps the skin to be protected from the dryness.

Nutritional Value per 100 gms

ENERGY (kcal)	CARBOHYDRATES (gms)	PROTEIN (gms)	FAT (gms)
579 kcal	21.55 gms	21.5 gms	49.9 gms

2. Cashewnuts

1. High in calories.100 gms of nuts provide 553 calories. They are rich in heart friendly MUFA's like oleic and palmitoleic acids. These essential fatty acids help lower LDL cholesterol while increasing good HDL cholesterol in the blood. There are many essential minerals such as manganese, potassium, copper, iron, magnesium, zinc and selenium. Selenium is an important micronutrient which functions as a cofactor for antioxidant enzymes such as glutathione peroxidases are of the most powerful antioxidants in the body. Copper is a cofactor for many vital enzymes including cytochrome C oxidase and superoxide dismutase. Cashews are also good in many essential vitamins such as pantothenic acid (Vitamin B5), Pyridoxine (Vitamin B6), riboflavin and thiamin (Vitamin B1). 100 gms nuts provide 0.147 mg or 32% of daily recommended levels of pyridoxine. Pyridoxine reduces the risk of homocystinuria and sideroblastic anemia.

* Drashti Kamdar, Nutritionist at Dr. Chandalia's Diabetes Endocrine Nutrition Management and Research Center (DENMARC) Mumbai.

Nutritional Value per 100 gms

ENERGY (kcal)	CARBOHYDRATES (gms)	PROTEIN (gms)	FAT (gms)
55 kcal	30.19 gms	18.22 gms	43.8 gms

Also cashews have antioxidant properties which help in preventing age related macular degeneration (ARMD) in the older adults.

3. Walnuts

Good source of energy and hold many health benefitting nutrients, minerals, antioxidants and vitamins that are essential for well being. Walnuts are rich sources of MUFA's which include linoleic acid, alpha linolenic acid and arachidonic acids. Regular consumption helps lowering LDL cholesterol and increases HDL cholesterol which is good cholesterol. Omega 3 fatty acids may help in cutting down coronary artery disease and strokes by favoring healthy blood lipid profile. Additionally they are rich source of many phytochemicals which can contribute to their overall antioxidant activity including melatonic, Vitamin E, carotenoids and polyphenolic compounds. These compounds are known to have a potential health benefit which prevents against cancers, aging, inflammation and neurological diseases.

Nutritional Value per 100 gms

ENERGY (kcal)	CARBO HYDRATES (gms)	PROTEN (gms)	FAT (gms)	CHOLESTEROL	DIETARY FIBER
654 kcal	13.7 gms	15.23 gms	65.21gms	0 mg	6.7 gms

4. Peanuts

Peanuts are rich in energy 567 kcal/100gms and contain health benefitting nutrients, minerals, antioxidants and vitamins that are essential for optimum health. They compose sufficient levels of MUFA especially oleic acid. MUFA helps lower LDL or bad cholesterol and increases HDL or good cholesterol level in the blood. Peanuts are good sources of dietary protein, compose fine quality of amino acids that are essential for growth and development. Peanuts contain high concentration of polyphenolic antioxidants primarily p-coumaric acid. This compound has been thought to reduce the risk of stomach cancer by limiting the formation of carcinogenic compounds or nitrosamines in the stomach. They are excellent source of resveratrol has been found to have a protective function against cancers, heart disease. Alzheimer's disease and viral/ fungal infections. Also resveratrol may reduce stroke risk through altering molecular mechanisms in the blood vessels (reducing susceptibility) to vascular damage through decreased activity of angiotensin a systemic hormone responsible for blood vessel constriction that would elevate blood pressure and by increasing production of vasodilator hormone, nitric oxide. The nuts are packed with many important B- complex groups of vitamins such as riboflavin, niacin, thiamin, pantothenic acid, Vit B6 and folates 100 gms of peanuts provide about 85% of RDI of niacin which contributes to health and blood flow to the brain. The nuts are a rich source of minerals like copper manganese, potassium, calcium, iron, magnesium, zinc and selenium.

Nutritional Value per 100 gms

ENERGY (kcal)	TOTAL FAT (gms)	CHOLESTEROL (mg)	SODIUM (mg)	CHO (gms)	DIETARY FIBER (gms)	PROTEIN (gms)
567kcal	49.2g	0	18	16.31	8.5	25.8

In general all the nuts are healthy foods and should be consumed in moderate amounts by all.

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MNT IN GESTATIONAL DIABETES MELLITUS

*Natasa Vora, Sheryl Salis**

Gestational diabetes mellitus (GDM) is defined as "glucose intolerance with onset or first recognition during pregnancy."[1] Pregnancy results in many changes in the body function and may affect the way the body controls blood glucose levels. During pregnancy, the placenta produces hormones that interfere with the action of insulin. In a normal pregnancy, a woman's pancreas compensates for this by making additional insulin. If the body is not able to meet the increased demand for insulin during pregnancy, blood glucose levels rise resulting in GDM. There is an exceptionally high estimated prevalence of GDM (27.5%) in India. India had the highest number of women affected by Hyperglycemia In Pregnancy with an estimated 5.7 million cases in 2013 followed by China with 1.2 million [2]

Presently, according to the Diabetes in Pregnancy Study Group of India(DIPSI) guidelines (2006) the target for glucose maintenance in GDM is at around 90 mg/dl in the fasting state, and around 120 mg/dl at 2 hours after starting the meal[3].All national and international guidelines suggest dietary management as the initial mainstay for the management of GDM

Medical Nutrition Therapy (MNT)

Medical nutrition therapy for GDM has been defined as a "carbohydrate-controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycemia, and the absence of ketosis."[4]

Goals of MNT in GDM

- To achieve normoglycemia
- To provide adequate weight gain, and add to the fetal wellbeing.
- To prevent ketosis

Energy: Women with GDM who are at ideal body weight (IBW) (0.8–1.2 times of their IBW) during pregnancy, the caloric requirement is 30 kcal/kg/day; for those who are overweight (1.2–1.5 times of their IBW), it is 24 kcal/kg/day; and for obese women (more than 1.5 times of their IBW), the caloric requirement is 12–15 kcal/kg/day of the present pregnant weight[1]. ADA Clinical Practice Recommendations have suggested a 30–33% calorie restriction for obese women with GDM, while advising a minimum 1800 calorie level[4]. For those women who are underweight (less than 0.8 of their IBW), the caloric requirementmay be up to 40 kcal/kg/day to achieve recommended weight gain.The days calorie requirement would normally range from 1800-2400 kcal[4].

Macronutrient distribution[1]

Carbohydrate	50%
Protein	20%
Fat	30%

Calorie and carbohydrate intake needs to be distributed across meals and snacks to blunt postprandial hyperglycemia, because it is the postprandial hyperglycemia that correlates with adverse pregnancy outcomes in GDM[4]. In GDM, breakfast sugars are the most difficult to control. In most GDM mothers, there is deficiency in first phase insulin secretion and due to the dawn phenomenon, there is more insulin resistance seen at the start of the day. As the pregnancy progresses, insulin resistance increases[5]. Studies have shown that distribution of calories especially at breakfast helps to achieve the glycaemic targets [6]. This implies splitting the breakfast into two i.e. eat half the portion, wait for an hour, test glucose levels and then eat the remaining half. This makes the carbs easier for the body to process, eating little and often and not requiring as much insulin to process the sugars. It is thus advisable that the first meal is low in carbohydrates and high in protein to avoid the undue spikes in post breakfast plasma glucose levels[5]

A meal plan for women with GDM typically includes three small to moderate sized major meals and three snacks[1].A bowl of curd, Cottage Cheese (paneer), Egg/Soya Nuts / Roasted Chana / Sprouts with veggies /Nuts can be a few low carbohydrate high protein snack options.

Carbohydrates:

Carbohydrates have the greatest impact on the blood glucose levels and hence total recommended carbohydrates are 50 % of total calorie intake daily[1]Postprandial blood glucose concentrations are directly dependent upon the

* **Natasha Kapre Vora, Sheryl Salis, Nurture Health Solutions, Mumbai**

carbohydrate content of the meal or snack.The quantity, quality and distribution of carbohydrate throughout the day affects blood glucose control. Choosing the right type and amount of carbohydrate is very important in maintaining glucose levels in the target range.Complex carbohydrates which are low GI like vegetables, whole fruits, whole pulses & sprouts, whole grain cereal should be preferred over high GI foods like polished rice, bread, refined flour and its products, cornflakes, potato, sugar, refined foods etc.

Fiber: Including fiber in the diet aids in improving satiety, preventing constipation which is commonly observed in pregnancy and stabilizing blood glucose levels. The recommended intake is 25-30g fiber /day[4]Inclusion of whole fruits, vegetables, and sprouts in daily diet can help to achieve adequate fiber intake.

Protein: Protein requirements increase in pregnancy (20% of total calories)[4] as they are the building materials of body responsible for growth, maintenance and energy. Proteins flatten the glycemic response of the food i.e they reduce glycemic index of food and hence help to control post prandial glucose spike.Protein intake with every meal is therefore recommended.

Fat:

30%of the total calories are recommended from fat sources[1].Consumption of oil, ghee, butter all included should be limited to 0.5kg/month/person. A blend of two or more vegetable oils should be used in daily cooking.

Diet should be low on saturated fats (<7%)[4]. Intake of biscuits, chips, cakes, pastries, processed fried, samosas, wadas, high fat Indian sweets and takeaway foods should be strictly avoided as they are a source of trans fat. Inclusion of omega 3 fatty acid rich foods such as Soybean, Canola/Rapeseed and mustard oils, walnuts, chia seeds, fish like mackerel, sardines, tuna and salmon should be encouraged for the fetal brain development.

Other nutrients

- Calcium requirements increase in pregnancy. Calcium rich foods such as low fat cow's milk ,curd and paneer, cheese, fish, green leafy veg , sesame seeds, finger millet (ragi) , amaranth (rajgira) should be included in the diet
- Increased iron requirements can be met by including iron rich sources like pearl millet (bajra), finger millet (ragi), rajma, green leafy vegetables with lime, egg with a citrus fruit like orange or sweet lime to enhance the iron absorption
- Include folic acid rich foods lik Amaranth (rajgira), mint, spinach, bengal gram, black gram, green gram, red gram, gingelly seeds, soya bean[4]
- Probiotics: Numerous studies show that probiotics can reduce the incidence of GDM. Probiotic use in pregnancy could significantly reduce maternal fasting glucose levels.Probiotic food supplements are available from many sources but effectiveness is dependent on various factors like temperature, anaerobic storage conditions, the initial dose of the strain and its quality[8]

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WHAT'S NEW?

INSULIN I DEG-ASPART (RYZODEG)

Ideg-aspart is a coformulated combination of two insulins; insulin degludec and insulin aspart. Insulin degludec is an ultra-long acting basal insulin. Its half life is about 24 hours and duration of action extends to 42 hours. This has been achieved by a very interesting series of alterations in the insulin molecule. The B 30 amino acid (threonine) is removed and the ß- chain lysine is attached to a glutamic acid spacer which links to a 16-carbon fatty di-acid.

Insulin aspart is already in use for more than a decade and is a rapid acting insulin analogue.

Coformulation is an important concept in insulin manufacture. Both the insulins present in the formulation preserve their original pharmacokinetic and pharmacodynamic properties and original profile of action. It is not possible to combine insulin glargine with a rapid acting insulin as insulin glargine is presented in a soluble form at pH 4 which precipitates in the body at pH 7.0 after injection. As the rapid acting analog is at a pH of 7.4, combination with glargine will form micro precipitate in the ampoule. Similarly, it is not possible to mix determir insulin and aspart.

Using I deg-aspart: In a type 2 diabetic uncontrolled with 3 types of OAD`s , a simple basal insulin is considered as the first step. Ideg-aspart offers additionally prandial insulin to cover one of two meals. Hence, treatment can be initiated by a single dose before the largest meal. If further required, intensification can be done by adding rapid insulin at the other two meals. Thus in most difficult cases, where 3 prandial and 1 basal injection is used (basal-bolus plan) I deg - aspart makes it possible to do the same job by using 3 injections instead of the 4 injections.

Ideg-aspart has also been used as two injections a day with good glycemic control.

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Hemraj Chandalia

QUESTION & ANSWERS

Q) What is the role of beta-glucans in diabetes?

Beta-Glucan is primarily cultured extract of Baker's yeast cell wall. It is used as an immunostimulant. Beta - glucans are sugar molecules (polysaccharides). It is found in cell walls of bacteria, fungi, yeast, algae, lichens and plants such as oats, barley, rye and wheat. Whole grains, mushrooms and yeast products are among the richest sources of beta-glucans.

Beta-Glucans helps in controlling diabetes in many ways such as:

1. Bacteria ferment beta-glucans release short chain fatty acids in the intestinal tract, which stimulates insulin release from the pancreas and alter glycogen breakdown by the liver. Therefore it plays an important role in glucose metabolism and protect against insulin resistance.
2. Consuming beta-glucan may increase the feeling of fullness and helps to eat less. It also delays empting of the stomach. This delaying causes glucose to be absorbed more slowly, limiting the spikes in blood glucose and insulin and decreases the appetite.
3. Beta-glucan combined with dietary changes and moderate exercise assist weight loss. As obesity is an important risk factor for diabetes, weight loss is essential for controlling type 2 diabetes levels, including its cure.
4. The major risk of diabetes mellitus is vascular or heart disease caused, by increased lipid levels and hypertension. Dietary intake of beta glucan has been shown to reduce all these risk factors.
5. Application of beta- glucans externally on skin can heal the diabetic ulcers.

Uses of beta glucans:

1. Beta-glucans are used for high cholesterol, diabetes, cancer and HIV/AIDS.
2. It is used to boost the immune system.
3. Beta-glucans are used for colds, flu, H1N1 flu, hepatitis, asthma, ulcerative colitis and rheumatoid arthritis.
4. Beta - glucans are applied to the skin for dermatitis, eczema, wrinkles, bedsores, wounds, burns and diabetic ulcers.

Tejal Shah

What are the symptoms of Hypoglycemia?

Hypoglycemia is defined as abnormal blood glucose levels below normal levels i.e. below 70 mg/dl in the blood also known as 'Whipple's Triad'.

- Symptoms known or likely to be caused by hypoglycemia especially after fasting or heavy exercise.
- Low plasma glucose measured at the time of the symptoms.
- Relief of symptoms when the glucose is raised to normal.

Normally Glucose is the main source of energy. When a meal is consumed it is taken up by the body cells through the blood stream. When person takes more glucose, excess glucose is stored in the liver in the form of Glycogen and stored in fat cells which can also be used as energy.

When blood glucose falls, another hormone produced by the pancreas - Glucagon stimulates the liver to breakdown Glycogen into glucose and release into the bloodstream to normalize sugar levels. But people with diabetes, because of impairment, other hormones i.e. epinephrine which is released into bloodstream increases the blood sugar levels which is not easily reduced even after ingesting insulin.

Hypoglycemia can be mild or severe. It can be treated easily or quickly after the consumption of carbohydrate rich food sources. But if not treated on time can be worse and cause dizziness, confusion, clumsiness. If it is progressed can lead to seizures, coma, eventually death.

When the blood glucose supply to the brain is reduced patient goes into Hypoglycemia which is detected by following symptoms:

- Neurogenic or Autonomic Symptoms
- Neuroglycopenic Symptoms

Neurogenic Symptoms: These symptoms occur due to certain glucose sensing areas in the brain which triggers the Autonomic or involuntary nerves as well as the Adrenal glands in the body. Symptoms are: Hunger, tingling sensation, shakiness, tremulousness, sweating, palpitations, nervousness, anxiety.

Neuroglycopenic symptoms: These symptoms occurs due to reduced glucose supply to the wide ranging parts of the brain resulting in confusion, drowsiness, fainting,

dizziness, difficulty in speaking, blurred vision, and finally unconciousness or coma. Neuroglycopenic Hypoglycemia is mainly caused by brain neuronal glucose deprivation.

Sypmtoms are: Irritability, confusion, difficulty in thinking, difficulty in speaking, Ataxia, Paresthesias, headaches, Stupor, seizures, coma, death.

Palak Parekh

Q) What are the acute complications of diabetes?

Hyperosmolar Hyperglycemic Nonketonic (HHNK) Syndrome

In this syndrome, there is extremely high blood glucose levels (>600-2000mg/dl), absence or only mild ketonemia and severe dehydration.

Treatment is hydration and small doses of insulin to correct hyperglycemia.

Hypoglycemia

Also referred to as insulin shock, is caused by an overdose of insulin or decrease in the available glucose caused by a delay in eating, missing a meal or loss of food by vomiting and diarrhoea, or increase in the exercise without accompanying modification of insulin dosage. Sulphonylureas can also cause hypoglycemia.

Symptoms:

Uneasiness, weakness, excessive perspiration, trembling, dizziness, headache, cold extremities, nervousness, blood sugars drop below 70mg/dl and coma when blood sugars drops below 40 mg/dl.

Treatment:

- Immediate treatment with carbohydrate If the blood glucose levels are below 70mg/dl, treat with 15 g of CHO, which is equivalent to 3 glucose tablets, 1/2 cup of fruit juice(125ml), sugar or honey- 1 tbsp.
- Wait for 15 minutes, if blood glucose levels remain less than 70mg, treat with another 15 g of CHO.
- Repeat testing and treatment until, blood glucose levels return to normal range.
- Evaluate the time to the next meal or snack, to determine the need of additional food. This drink or snack should give 15-20g of CHO.

Ketoacidosis

It is a state of severe insulin deficiency .

It is characterised by :

- acid-base imbalance
- fluid imbalance
- dehydration
- circulatory and renal failure
- hyperglycemia leading to glucosuria which increases the osmotic load causing sodium and water loss
- due to insulin deficiency there is increased mobilization of lipids leading to
- ketonemia, ketoacidosis and finally coma
- blood sugars between 350-850 mg/dl

Symptoms:

Polyurea, polydipsia, polyphagia, dry mouth, flushed face, vomiting, nausea, abdominal pain, fruity odour in breath.

Treatment:

1. Insulin therapy
2. Electrolyte and fluid replacement.
3. intra - venous administration of saline + bicarbonate to maintain water and acid base balance .

   oral intake is avoided for the first 24 hours, to avoid vomiting and aspiration.

   oral intake may start with fluids , followed by the transition to the routine hospital diets .

Divya Jain

WHAT'S COOKING ?

PIZZA PARATHA

INGREDIENTS	AMOUNT
Ragi flour (nachni atta)	30 gms
wheat flour (*gehun ka atta*)	30gms
Grated cottage cheese (paneer)	10 gms
Chopped Onions	10 gms
Chopped tomato	10 gms
Boiled and grated carrot	10 gms
Boiled Peas	1/4 th tsp
Boiled corn	1/4 th tsp
Carom seeds (*ajwain*)	1/4 th tsp
Cumin seeds (*jeera*)	1/2 tsp
Dried mango powder (*amchur*)	1/4 th tsp
Cooking oil	1 tbsp
Finely chopped green chillies	1 tsp
Finely chopped coriander leaves	1 tbsp
Dried basils	1 tbsp
Salt	To taste

METHOD OF PREPARATION:

- In a large bowl, combine the Ragi and wheat flour, carom seeds, cumin seeds, dried mango powder, salt and oil. Knead into smooth and soft dough, using a little water.
- Cover the dough and set it aside for 15 to 20 minutes. After that, divide it into 2 balls, flatten them a little and keep them aside.
- In another bowl, combine all the ingredients for the filling
- Roll out the dough into 2 rotis. Spread the filling on one and place the other roti on the top of it and seal the edges.
- Heat a griddle (*tava*) and cook the paratha until both sides are done.
- Serve hot.

Serves: 1
Nutritive value for 1 serving:

Energy	Carbohydrates	Protein	Fat	GI
274.7	39 gms	9.5 gms	3.5 g	55

MIXED BEANS SALAD

INGREDIENTS	AMOUNT
Mixed boiled beans (Rajma, Chawli and Chick pea)	1/4th cup
Sweet Corn	1/4th cup
Spring Onions	1/2 cup
Tomato cubes	1/2 cup
Green chillies (finely chopped)	1 tsp
Coriander chopped	1 tbsp
Lemon juice	2 tbsp
Chat masala	1 tsp
Black salt	1/4 tsp
Salt and Pepper	To taste

METHOD OF PREPARATION:

Combine all the ingredients in a deep bowl and mix well. Refrigerate for 1 hour and serve chilled.

Serves: 1
Nutritive value for 1 serving:

Energy	Carbohydrates	Protein	Fat	GI
200 kcal	58 gms	10.2 gms	1.4 g	50

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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.

C. Munichoodappa. F.R.C.P.C.
Diplomate, American Board in Internal Medicine
Bangalore
Email id: dr.munichoodappa@gmail.com

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(104, Lady Ratan Tata Medical Centre, M.Karve Road, Mumbai)

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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.

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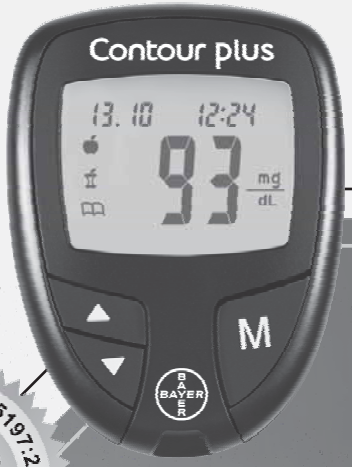
Bayer HealthCare

ACCURACY
YOU CAN TRUST

- **Meets the ISO 15197 : 2013 accuracy requirements** [1,2,3]
- **Second Chance™ Sampling # : allows the patients to reapply blood to the same test strip if the first sample was not enough**[3]
- **Easy – to – teach features and has Basic mode (L1) and Advanced mode (L2)**[3]



Meets the ISO 15197:2013 accuracy requirements
ISO 15197

HIGHLY AC CURATE

\# Within recommended testing time

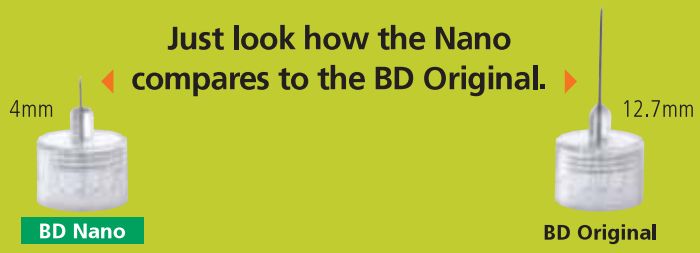
References :
1. ISO 15197:2013 standard
2. Goldy et.al.International conference on Advanced technologies and Treatments for Diabetes 2013
3. Bayer. Data on file

For more information : Contact Customer care : 1800 123 0123 or Visit us : http://diabetes.bayer.in
Bayer Pharmaceuticals Pvt Ltd, Central Avenue, Hiranandani Estate, Thane (W) - 400607

Shorter, thinner and effective for patients of all sizes.[1]

Introducing the NEW 4mm x 32G
BD Ultra-Fine™ Nano Pen Needle.

Just look how the Nano compares to the BD Original.



BD

Helping all people live healthy lives

72% of patients who tried the new BD Nano preferred it over their current pen needle.[2]

Proven effective for patients of all sizes[3]

- Clinically proven effective in maintaining glycemic control for patients of all sizes[4]
- Provides predictable insulin absorption, same as the 8mm and 5mm
- No increased leakage when compared to the 8mm and 5mm

Proven less painful, delivers a more comfortable injection[5]

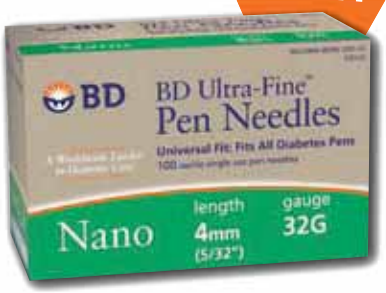
- 64% of patients found the 4mm pen needle to be more comfortable than both the 8mm and 5mm

Shown to be less intimidating[6]

- 88% of the patients reported feeling "not at all anxious" after seeing the 4mm pen needle

BD Nano fits all pens sold in the US.[7]

New!



Needles are actual size.

NDC/HRI# 08290-3201-22

You can dispense the new BD Nano to ALL patients!

The skin is no more than 2.8mm thick in nearly all patients.[8]

The 4mm x 32G BD Nano:

- Reduces the risk of IM injections
- Allows for "no-pinch" technique for all patients
- Provides more injection site flexibility

"No-pinch" technique
Inject "straight in," flush with skin for easy injection.at all sites

For comfortable Insulin Injection Experience

℞
BD Ultra-Fine™ III
4mm/32G Nano Pen Needle

Smallest pen needle ever

For more information, visit www.bd.com/hcp/nano.

1,3,5. Hirsch LJ, Gibney MA, Albanese J, et al. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. *Curr Med Res Opin*. 2010; 26 (6): 1531–1541.

2,6. Data on File.

4. Tested with adults of BMI 20-49.

7. As of April, 2010.

8. Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. *Curr Med Res Opin*. 2010; 26 (6): 1519–1530.

BD

BD Medical - Diabetes Care
Becton Dickinson India Pvt. Ltd.
5th & 6th Floor, Signature Tower -B,
South City - 1, Gurgaon - 122001
Tel: 91-124-3088333
Fax: 91-124-2383224/5/6
Website: www.bd.com/india
Email: bd_india@bd.com

My **NEW** Diabetes Therapy
helps me Control HbA1c & lose weight

NOVEL ß-CELL INDEPENDENT MOA[1]

UNSURPASSED EFFICACY
Compared to Glimepiride and Sitagliptin, INVOKANA® 100mg is non-inferior[2,3]
INVOKANA® 300mg is superior[2,3]

SUSTAINED & SIGNIFICANT WEIGHT LOSS[3,4]

HYPOGLYCEMIA COMPARABLE TO PLACEBO[5]

Invokana®
canagliflozin tablets

A CLASS APART

References:

1. INVOKANA® India Prescribing Information (January 2014) **2.** Lavalle-González FJ et al. Diabetologia. 2013;56(12):2582-92 **3.** Cefalu WT et al. Lancet 2013;382(9896):941-50 **4.** Leiter LA et al. Diabetes Care. 2014. **5.** Stenlöf K et al. Diabetes Obes Metab. 2013;15(4):372-82.

For the use of a Registered Medical Practitioner or a Hospital or Laboratory Canagliflozin tablets 100mg / 300mg
INVOKANA®

Composition and Strength: Canagliflozin 100 mg / 300mg. Each 100 mg tablet contains 102 mg Canagliflozin hemihydrate, equivalent to 100 mg Canagliflozin. Each 300 mg tablet contains 306 mg Canagliflozin hemihydrate, equivalent to 300 mg of Canagliflozin. **Pharmaceutical form:** 100 mg - The tablet is yellow, capsule-shaped, immediate-release and film-coated, with "CFZ" on one side and "100" on the other side. 300 mg - The tablet is white, capsule-shaped, immediate-release and film-coated, with "CFZ" on one side and "300" on the other side. **Therapeutic Indications:** INVOKANA® is indicated as an adjunct to diet and exercises to improve glycemic control in adults with type 2 diabetes mellitus as monotherapy and combination therapy. **Dosage and Administration:** The recommended starting dose for adult > 18 years is 100 mg or 300 mg once daily orally preferably before the first meal of the day. A starting dose of 100 mg once daily should be used in patients on loop diuretics and patients ≥ 75 years of age. In patients with an eGFR 45 mL/min/1.73 m2 to < 60 mL/min/1.73 m2, the dose of INVOKANA® is limited to 100 mg once daily. The 300 mg dose may be considered for patients with an eGFR > 60 mL/min/1.73 m2, who need tighter glycemic control and who have a low risk of adverse reactions associated with reduced intravascular volume with INVOKANA® treatment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** INVOKANA® has not been studied in pediatric patients (< 18 years), patients with type 1 diabetes and is therefore not recommended for use. INVOKANA® should not be used for the treatment of diabetic ketoacidosis or in patients with an eGFR < 45 mL/min/1.73 m2 [CrCl < 45 mL/min], as it would not be effective in these settings. In patients with evidence of reduced intravascular volume, correcting this condition prior to initiation of INVOKANA® is recommended. **Drug Interactions:** The metabolism of INVOKANA® is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4. If a combined inducer of these UGTs and drug transport systems (e.g., rifampicin, phenytoin, barbituates, phenobarbitol, ritonavir, carbamazepine, efavirenz) must be co-administered with INVOKANA®, monitor HbA1c in patients receiving INVOKANA® 100 mg once daily with consideration to increasing the dose to 300 mg once daily if additional glycemic control is needed. INVOKANA® neither inhibits cytochrome P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, or CYP2E1, CYP2B6, CYP2C8, CYP2C9, nor induces CYP1A2, CYP2C19, CYP2B6, CYP3A4 at higher than therapeutic concentrations. INVOKANA® is a P-glycoprotein (P-gp) substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately. **Pregnancy, Breast-feeding and Fertility:** There are no adequate and well-controlled studies in pregnant women. INVOKANA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known if INVOKANA® is excreted in human milk. A risk to the breast-fed child cannot be excluded. The effect of INVOKANA® on fertility in humans has not been studied. **Adverse reactions:** In clinical studies of INVOKANA® the most commonly reported adverse reactions during treatment (≥ 5%) were vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria. Other adverse reactions in clinical studies of INVOKANA® that occurred at a rate < 2% in placebo-controlled studies were adverse reactions related to reduced intravascular volume (postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope), skin rash, and urticaria. In the event of an overdose, it is reasonable to employ the usual supportive measures, including monitoring of vital signs and observation of clinical conditions. **Overdose:** Single doses up to 1600 mg of INVOKANA® in healthy subjects and INVOKANA® 300 mg twice daily for 12 weeks in patients with type 2 diabetes were generally well-tolerated. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.
Storage: Store below 30°C and in dry place. Protect from light. Keep out of reach of children.

Warning: To be sold by retail on the prescription of Registered Medical Practitioner only. Version: CCDS 09 Jan 2014
For complete prescribing information, please contact: Johnson & Johnson Private Limited, Arena Space, Behind Majas Depot, Off J.V. Link Road, Jogeshwari (E), Mumbai 400060

INV/33/LBL/05.15/Q2.15-Q4.15

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