Vol 1, No 1, Jan - Mar, 2013

Journal of Diabetes Education

To Dispel Darkness Of Diabetes

DIET MANAGEMENT

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Association of Diabetes Educators
(India)

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IN.GLA.12.09.14

JOURNAL OF DIABETES EDUCATION

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Vol. 1 **Number 1** **Jan- Mar, 2013**

The association is supported by unrestricted educational grants from BD, Novo Nordisk Pvt. Ltd, Novartis, Sanofi Aventis

The journal is supported by unrestricted educational grants from Becton, Dickinson and Company (BD)

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Hemraj B. Chandalia

Diabetology in India

Until about 1950's, diabetes was managed by internists (consultant physicians) all over the country. An insight into diabetes and its complications required a thorough knowledge of internal medicine. Hence, physicians with good clinical command of heart, kidney, eye and neurological diseases practised diabetology. In 1950's the first few Diabetes Clinics appeared on the scene; Dr. R.V. Sathe and Dr. N.G.Talwalkar in Mumbai and Dr. Vishwanathan in Chennai pioneered this movement. Dr. R.V. Sathe was the Honorary Professor of Medicine at the Grant Medical College and later, Vice Chancellor of University of Bombay. A man of great integrity And a widely acclaimed teacher, he initiated Diabetes Clinic at the Grant Medical College, which was later developed by Dr. N. G. Talwalkar and later headed by the present author. This spans a period of about 50 years. Dr. S. S. Ajgaonkar was another pioneer, who closely worked with Dr. Sathe on a number of Ayurvedic compounds in diabetes, the most notable being Jasad Bhasma and Mamejo. Dr. S.S. Ajgaonkar was a great diabetes educator who pioneered patient-education in India. He founded the Diabetic Association of India which continued to be an active organisation till the end of the last century. Dr. N. G. Talwalkar took over the mantle from Dr. R. V. Sathe. He was a great human being, a fine physician and teacher.

Additionally, he had a great interest in the history of medicine and more specifically, the history of Grant Medical College and J.J. Hospital. The present author had the privilege of getting Dr. Talwalkar's serial articles on the history of Grant Medical College published in a book form "Man and Memorabilia of Grant Medical College and J.J. Hospital", a book which has served as a collector's item. Dr. M. Dhirwani was another great physician, who devoted his time only to diabetes. Dr. J.C. Patel was another eminent physician, a professor at the KEM hospital, who had the capacity to master two unrelated subjects, Hematology and Diabetes successfully.

He founded the Diabetes Clinic and Hematology Clinic at the KEM Hospital and Bombay Hospital. These Clinics are functional to this day And making great contributions to patient care and research. In the next decade, i.e. in 1960's, specialized training in Endrocrinology and Diabetology became available at a few selected centers in India. As Bombay lagged behind in this respect, most Endocrinologists and Diabetologists received their training in UK or USA after completion of their MD degree. Later on, the DM (Endocrinology) was introduced in the Mumbai University.

In 1970's, the present author came in contact with Prof. MMS Ahuja, Professor of Endocrinology at the All India Institute of Medical Sciences, Delhi. He was a great academician and researcher. He founded the Research Society for Study of Diabetes in India (RSSDI), a society which has grown from strength to strength and currently has about 5500 physicians and diabetologists as its member. Dr. B.B. Tripathy of Cuttack and Dr.O.P.Gupta of Ahmedabad were co-founders of RSSDI. RSSDI was ably expanded by the efforts of Dr. P.V. Rao at Nizam's Institute at Hyderabad. RSSDI has published a textbook of diabetes, editedby Dr. B.B. Tripathi and 6 other editors. This book is undergoing publication of its third edition and has made a clear niche in India and the developing world.

The society publishes a journal, International Journal of Diabetes in developing countries for the past 32 years, earlier edited by MMS Ahuja and later jointly by Dr. Ahuja and the present author. In the eighties,a method of estimating glycosylated hemoglobin was described by Fluckiger in Germany. This was rapidly adopted by Dr. P.R. Krishnaswamy, Chief Biochemist and the present author at the Jaslok Hospital. Dr. P.R. Krishnaswamy is a brilliant biochemist, currently working in Banglore. The glycosylated hemoglobin method was fully developed and indigenized by them and several basic aspects of this test led them to publish 6 original articles around that time.

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The Southern part of India, especially Chennai saw an early and rapid development of Diabetology under Dr. Vishwanathan and Dr. Sam Moses. Dr. Vishwanathan's diabetes center was later managed by Dr. Ramchandranand and Dr. V. Mohan and Dr. Vijay Vishwanathan. These centers produced valuable epidemiological data.

These diabetologists continue to work vigorously. Dr.V. Mohan is the most well known diabetologist, researching and publishing prolifically at present. He has expanded the patient-care to several cities of India.

Currently, the subspecialty of diabetology is developing rapidly in India. Those doing DM (Endocrinology) are well trained in diabetology; many universities have instituted a Diploma in Diabetology; some of these courses are well- structured, others are offering the Diploma primarily from distance education and with minimal effort on the part of the student. Many consultant physicians are looking after diabetic patients, at times with some extra training and experience. As the number of diabetics in India is high, they perceive a good opportunity in Diabetology. Needless to say, the quality of the education and training needs to be well controlled.

A large number of basic physicians (MBBS) are also being trained in Diabetology. Diabetes educators will form another important work-force in Diabetology. Any effort that leads to improve the quality of life of a person with diabetes is to be appreciated.

Diabetes Education in India

It is so exciting and interesting to educate people with diabetes and arm them with knowledge and tools to live a happy life with diabetes. I have always enjoyed this and my team of nutritionists and educators have done this with great enthusiasm and fervour.

I started my career as Endocrinologist and Diabetologist in Bombay in 1971, on my return from USA after four years of training and later teaching experience at the University of Alabama Medical Center in USA. I maintained a great interest in patient-education in diabetes. I regularly lectured under the aegis of Diabetic Association of India at its monthly sessions. This was started by Dr.S.S.Ajgaonkar and was a continuing activity for many decades.

Nutritionists were not called upon to participate in patient education in 1970's in Bombay. In one of the private hospitals even in 1980's my request for appointing a nutritionist was met by a curt reply by the management: "we don't need a dietician; we have a wonderful kitchen where we only use pure ghee. However, if you wish to appoint a dietician, you may proceed by providing her salary from your funds". Needless to say, I went ahead with this and after 5-10 years the hospital realised the usefulness of this class of paramedics in patient education. I was at this hospital only for a year but watched with great interest the changing perceptions of the management.

I started appointing a Nutritionist at my center in 1975 and continued to do so all along. Currently, we employ 4-5 nutritionists, who also serve as diabetes educators. We linked with Dr.Shobha Udipi, Director SNDT about 3 years ago and started a full 16 credit, 6 month certificate course in Diabetes Education at the SNDT University. This is the first University-linked well administered, well structured Diabetes Educators Course in India. The course is running well and expanding. We have plans to convert it into a 32 credit, 1-year Diploma Course in Diabetes Education. We are also planning to make this course web based so that we can prepare a cadre of diabetes educators through distance education, who will gain practical experience through local clinics. I firmly believe that this will help empower people with diabetes to look after their problems.

Diabetes Educators training has to be of very high standard, monitored by an University. Although many associations, institutions and pharmaceutical industries participate in this process, they award a certificate after merely 3 days of training, thus giving a false aura of expertise.

It is not easy to motivate people to learn. Although it concerns their life so seriously, people with diabetes often suffer from apathy, despondency, scorn and skepticism, and do not want to be educated about their disease. I have known a PhD in Chemistry measuring U40 insulin in U100 syringe incorrectly. On the other hand, we know that knowledge and wisdom are two different attributes and we published data thirty years ago in Diabetes Care that it is possible to educate illiterates or semiliterates about their disease.

The movement of patient education was quite active in Mumbai, Delhi, Chennai and Kolkata.

Dr. S.S. Ajgoankar in Mumbai, Dr. Vishwanathan in Chennai, Dr. Sen Gupta in Kolkata and Dr. MMS Ahuja and Dr. Hari Vaishnav in Delhi pioneered this

movement. In Mumbai, we started a monthly session at our center about 30 years ago; this is continuing till today.

We started a quarterly magazine, Diabetes Today, which is in its twenty-second year of regular publication. We have held several large exhibitions in Mumbai; one at Somaiya College ground and another about 3 years ago at the Nehru Centre. These were well attended. My colleagues, Dr.Vijay Paniker, and Dr.P.S.Lamba contributed heavily to make them successful. A musical devised by Dr. Vijay Paniker was a very popular teaching tool at these exhibitions. Dr.Negalur activated an Association started by us, Association for Diabetes Care and Prevention, which is very active in the Thane-Dombivali-Kalyan area.

A very significant move occurred in Diabetes Education by the advent of a well-structure, International Diabetes Federation recognized 6 month course under the aegis of Project HOPE. This project has trained about 2500 educators in the country.

Much more needs to be done in this area. We need more than 20,000 well trained diabetes educators in India. We need to put up an Association of People with Diabetes, who should spearhead an educational movement and also be able to lobby for their rights to employment, insurance and good health-care. We need to expand our magazine, Diabetes Today into a multilingual magazine available freely at magazine stalls.

Education is the key to lifestyle diseases. Obesity and diabetes is more effectively tackled by education than by any drugs or nutraceuticals. Education needs less expensive in-puts but provides great benefits to the recipients. Medical profession is always keen on education, even if it cuts its own roots, because it continues to be a noble profession!

Establishment of an Association of Diabetes Educators from Mumbai is a very significant move in this direction. We hope that this association will later demand formation of a Council for Diabetes Education, so that a professional status is given to this group of health-care workers.

■

Gestational Diabetes Mellitus

Sunil Gupta

Introduction

The worldwide prevalence of type 2 diabetes mellitus (T2DM) is rising rapidly. Global prevalence of diabetes in 2011was 366 million; by 2030 this will have risen to 552 million. The number of people with type 2 diabetes is increasing in every country. 80% of people with diabetes live in low- and middle-income countries. The principal driver for this increase is thought to be the worldwide rise in the prevalence of obesity, combined with ageing populations and a trend towards urbanization.[1]

While all these factors contribute to the epidemic of diabetes, intrauterine environment is emerging as a potential risk factor. The "fetal origin of adult disease" hypothesis proposes that gestational programming may critically influence adult health and disease.[2] Gestational programming is a process whereby stimuli or stresses occurring at critical or sensitive periods of fetal development, permanently change structure, physiology, and metabolism, which predisposes individuals to disease in adult life.[3] If the stimulus happens to be glucose intolerance in pregnancy, it predisposes the offspring to an increased risk of developing glucose intolerance in the future. This vicious cycle is likely to influence and perpetuate the incidence and prevalence of glucose intolerance in any population.4 Therefore, preventive measures against type 2 diabetes should start during the intrauterine period and continue from early childhood throughout life.[5] Thus detection of gestational diabetes mellitus is an important public health issue.

Definition & Prevalence

Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. Gestational diabetes mellitus (GDM) as defined by the American Diabetes Association (ADA) and the World Health Organization (WHO) is ''any degree of glucose intolerance with onset or first recognition during pregnancy'', irrespective of the treatment with diet or insulin. Prevalence varies from 2 to 10%, and sometimes much higher, depending on the population being tested and the diagnostic criteria being used. The prevalence of GDM ultimately reflects the background rate of type 2 diabetes. There has also been an increase in the rate of GDM over the last generation, possibly related to lifestyle factors as well as better case ascertainment.[6,7]

A South Indian study showed the prevalence to be 13.9%. It was 17.8% in Urban, 13.8% in semiurban and 9.9% in rural Indian women.8Among the women with GDM, 12.4% were detected within 16 weeks of pregnancy, 23% between 17 and 23 weeks, and the remaining 64.6% at more than 24 weeks of pregnancy. The mean age of the pregnant women screened in the urban, semi-urban, and rural areas was 23.7± 3.55 years, 23.4±3.30 years, and 22.5±3.09 years, respectively. There was a consistent increase in the prevalence of GDM in all 3 areas as BMI increased, and the trend was statistically significant (P <0.0001) Among the women with GDM, the highest prevalence was observed in women with a BMI greater than 25, with28.4% in the urban area, 23.8% in the semi-urban area, and 16.1% in the rural area. The prevalence of GDM was 7% higher in women with a BMI greater than 25 compared with women with a BMI between 23.0 and 24.9 in urban and semi-urban areas; The prevalence of GDM in the physically inactive group was 19.1%, 16.6%, and 12.1%, whereas it was 17.6%, 12.8%, and 9.7% in the physically active group in the urban, semi-urban, and rural areas, respectively. A positive family history of diabetes mellitus was present in 25% of the women with GDM in the urban, 19.2% in the semi-urban, and 14.1% in the rural area. There was a significant association (P<0.001) between family history of diabetes mellitus and the occurrence of GDM among pregnant women. [Fig 1,2,3,4]

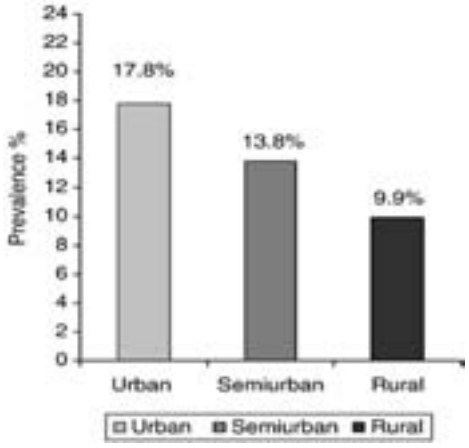

Fig. 1. Prevalence of gestational diabetes mellitus by area[8]

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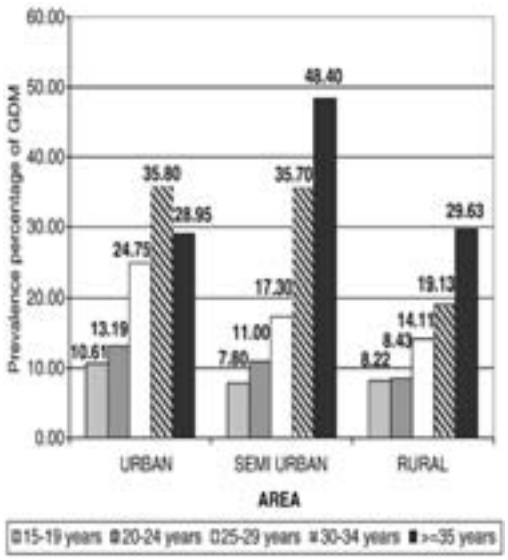

Fig. 2. Prevalence of gestational diabetes mellitus by age group [8]

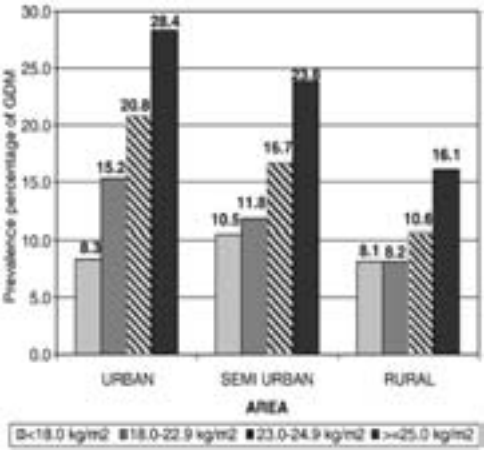

Fig. 3. Prevalence of gestational diabetes mellitus by body mass index (calculated as weight in kilograms divided by height in meters squared).[8]

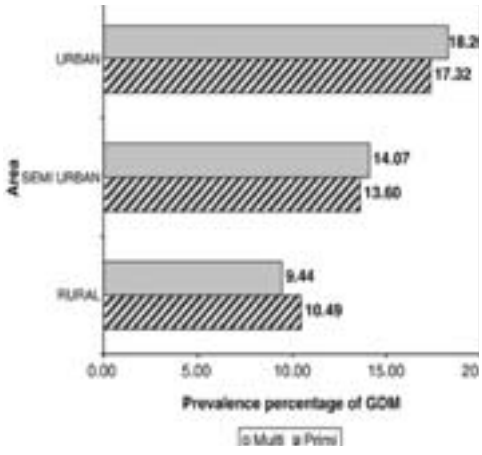

Fig. 4. Prevalence of gestational diabetes mellitus by gravidity.[8]

Based on univariate analysis, author observed in all 3 areas that age greater than 25 years, BMI greater than 25, and family history of diabetes were significantly associated with the prevalence of GDM. Based on multiple logistic regression analysis taking all 3 areas into consideration, family history and BMI greater than 25 were found to have a significant independent association (P<0.001) with GDM.[8]

Significance of GDM

GDM is associated with a trilogy of risks. Significant pregnancy complications including increased perinatal morbidity and possibly mortality can occur.[9,10,11] A diagnosis of GDM also identifies a mother at high risk for the future development of type 2 diabetes. The effects of maternal hyperglycemia (of any kind) are associated with the development of metabolic problems including type 2 diabetes in the offspring.[12] It is, perhaps, for this effect of intrauterine programming that the disorder is most worthy of detection. It has now been demonstrated that the treatment of GDM improves pregnancy outcomes. In the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), the incidence of serious perinatal complications (a composite of death, shoulder dystocia, nerve palsy, and fracture) was 4% among women randomized to routine care compared with 1% among the intervention group.The number of GDM cases that needed to be treated to prevent one serious perinatal complication was 34. This indicates that excess serious perinatal complications will occur in 3% of cases of untreated or unrecognized GDM. It is utmost important to understand that the failure to identify a woman with GDM denies her the opportunity to have treatment for potentially preventable serious fetal complications.

Glucose Metabolism and Gestational Diabetes

In normal pregnancy, directly or indirectly, the growth of the fetal-placental unit increases cortisol, growth hormone, human placental lactogen, estrogen, progesterone, and prolactin, which in concert lead to hyperinsulinemia, insulin resistance, fasting hypoglycemia, and postprandial hyperglycemia. A progressive transition of fuel sources occurs so that by the third trimester, the metabolic fuel to meet the demands of the fetus changes from predominately maternal carbohydrate to fat. Pregnancy is characterized by increased and adaptive pancreatic beta-cell function to compensate for decreased insulin sensitivity and increased requirements.

Morphologically, maternal pancreatic hypertrophy and hyperplasia occur. In response to elevated insulin levels, peripheral muscle glucose utilization and tissue glycogen storage increase in an effort to maintain normal insulin sensitivity in the first trimester of pregnancy. As gestation advances, these responses become inadequate to meet the energy requirements of the fetus, and insulin resistance develops. Insulin resistance in normal pregnancy is estimated to increase by 40% to 70%, predominately in the third trimester. In a longitudinal study of healthy pregnant women using the hyperinsulinemic-euglycemic clamp, Catalano and colleagues[13] found a 56% decrease in insulin sensitivity in nonobese women by late pregnancy. Using the euglycemic-hyperinsulinemic clamp, Sivan and colleagues[14] demonstrated that healthy women developed insulin resistance mostly in the third trimester and showed a 40% reduction in peripheral glucose uptake by muscle in the third trimester compared with the nonpregnant state. Furthermore, the reduction in insulin sensitivity was compensated by reciprocal increase of the first and second phase insulin response.[15]

There seems to be no significant change in insulin receptor binding in pregnancy; thus insulin resistance in normal pregnancy is likely related to postreceptor handling of glucose. Postreceptor mechanisms contributing to insulin resistance include, impaired tyrosine kinase activity, which is normally responsible for the phosphorylation of cellular substrates; decreased expression of insulin receptor substrate-1, a cytosolic protein that binds phosphorylated intracellular substrates and transmits signals downstream; and decreased expression of the GLUT4 glucose transport protein in adipose tissue, which promotes glucose uptake. The cytokine tumor necrosis factor α and leptin may also be involved in insulin resistance seen in normal pregnancy.

Compared with normal pregnant women, women with GDM have impaired beta-cell function and reduced beta-cell adaptation resulting in insufficient insulin secretion to maintain normal glycemia. Women with GDM, and more so obese women with GDM, have greater insulin resistance and less endogenous hepatic glucose production than non-GDM women. People noted a more profound drop in tyrosine kinas activity in women with gestational diabetes when compared with healthy normal women, suggesting a postreceptor mechanism abnormality as at least one cause of the increased insulin resistance in GDM.[15]

Pregnancy-induced insulin resistance unmasks the beta-cell defects, which underlie GDM. These defects range from beta-cell dysfunction secondary to autoimmune factors or chronic insulin resistance or highly penetrant genetic abnormalities of insulin secretion.

Screening and diagnosis of GDM: the IADPSG consensus statement on the diagnosis of hyperglycaemia in pregnancy

Until recently, there has been a lack of international consensus on the screening and diagnosis of GDM. The various diagnostic criteria used were not based on the prediction of adverse pregnancy outcomes, but on the prediction of the risk of diabetes after pregnancy or on the OGTT diagnostic criteria for impaired glucose tolerance and diabetes in the non-pregnant population. The HAPO study was designed to determine the actual levels of blood glucose during a 75-g OGTT performed between 24 and 32 weeks of pregnancy, lower than that of overt diabetes, that predicted adverse perinatal outcomes. The study showed a continuous relationship between maternal glycaemia and the adverse pregnancy outcomes of LGA babies, primary caesarean section, clinically defined neonatal hypoglycaemia and cord C-peptide >90th percentile.. It is important to also add that the HAPO findings are consistent with other studies that show a relationship between mildly elevated blood glucose levels and adverse outcome. To translate the HAPO study data into clinical practice, an IADPSG consensus panel (with representatives from the 10 member organisations) met in 2008 to make recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. The IADPSG diagnostic criteria for GDM are shown in (Table 1).

Important points to make about the IADPSG consensus statement on the diagnosis of GDM are the following. Selective screening based on risk factors for GDM has not been recommended. Screening by a glucose challenge test (GCT) is not recommended, as the GCT does not detect women with fasting hyperglycaemia only. Thus, all women without an earlier diagnosis of GDM or diabetes are recommended to have a 2 h OGTT at 24–28 weeks of pregnancy. Based on the HAPO cohort, the proposed IADPSG diagnostic criteria diagnose about 17.8% of women as having a hyperglycaemic disorder of pregnancy.[16]

Table 1: Diagnostic Criteria

Diagnostic criteria for GDM[17, 18, 19]

	Glucose load	Glucose tolerance test (mg/dl)				Abnormal values for diagnosis
		Fasting	1 hour	2 hours	3 hours	
ADA	75 g	95	180	155		Two or more
	100 g	95	180	155	140	Two or more
ADIPS	75 g	100	–	145		One
CDA	75 g	95	190	160		Two or more=GDM One Value=IGT of Pregnancy
WHO	75 g	126	–	200		One
DIPSI	75 gm Glucose	–	–	140	–	One
IADPSG	75 gm OGTT	> 92	> 180	> 153		One

Abbreviations: ADA, American Diabetes Association; ADIPS, Australasian in Pregnancy Society; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; WHO, World Health Organisation, DIPSI- Diabetes in Pregnancy Study Group in India; IADPSG- International Association for Diabetes in Pregnancy Study Group.

As discussed above, the IADPSG panel also recommended a screening test to be performed at the first prenatal visit to avoid late diagnosis of pre-existing overt diabetes. The panel stated that this could be for all women or could be a selective screen in high-risk women. Many of the IADPSG panel favoured using the HbA1c test for this screen, but the use of fasting plasma glucose or random blood glucose was suggested as alternative options if HbA1c testing is not feasible. A HbA1c > 6.5% is now accepted to be diagnostic of diabetes in non-pregnant individuals by the American Diabetes Association, with the range of 5.7–6.4% being considered to be indicative of pre-diabetes. however, they did not suggest HbA1c levels for diagnosis of GDM on the first antenatal visit screen.[16]

The recommended IADPSG approach to diagnosis and classification of hyperglycaemic disorders of pregnancy is a major advance. First, the new diagnostic criteria are linked to the risk of adverse pregnancy outcomes. Second, the issue of late diagnosis of overt diabetes in pregnancy has been addressed. Third, it promotes a uniform approach to enable international comparison of GDM prevalence and pregnancy outcomes. A very significant issue that needs to be addressed by all health services adopting these recommendations, however, is the increased numbers of women that will be diagnosed (up to a doubling depending on old criteria used and local prevalence). This will place enormous strain on health-service personnel and costs, if not carefully addressed.[16]

DIPSI Criteria

Diabetes In Pregnancy Study group in India (DIPSI) has laid down a very simplified diagnostic criteria for GDM19, which follows more of the WHO Criteria (Table 2). If 2hr post 75gm OGTT value is > 140mg%, it is diagnostic of GDM and if 2hr value is between 120 to 140mg% it is classified as Decreased Gestational Glucose Tolerance (DGGT). Both category of patients need treatment & follow up.

Table 2:

With 75 gm OGTT	In Pregnancy
2 hr ≥ 140 mg/dl	GDM
2 hr -120-139 mg/dl	DGGT *

* Decreased Gestational Glucose Tolerance

Management of GDM: is our current approach improving both the short- and long-term outcomes?

There has been major progress in recent years with respect to the management of GDM. The ACHOIS and MFMUN-GDM (Maternal and Fetal Medicine Units Network-GDM) studies show that the standard approach of diagnosis at 24–32 weeks, dietary advice, self-monitoring of blood glucose and insulin therapy, as needed, can improve short-term (perinatal) outcomes.[20,21] Randomised controlled trials (RCTs) of the use of glibenclamide (glyburide) (published 2000) and metformin (published 2008) versus insulin in GDM pregnancy were favourable for their use with respect to perinatal outcomes. None of the above studies, however, considered long-term outcomes.

Management targets in GDM

The 5th International Workshop Conference on GDM made recommendations relating to targets for glycaemia during GDM pregnancy, and the potential role of fetal growth targets.[22] The workshop recommended maintaining capillary blood glucose at <96 mg /dl in the fasting state, <140 mg /dL) at 1 h and <120 mg/ Dl at 2 h after starting a meal.[17,18] These targets were based on the then knowledge of normal glycaemia in pregnancy and the outcomes of the ACHOIS study. They commented that data from controlled trials of lower versus higher targets were lacking. Careful analysis of the metformin versus insulin in gestational diabetes study (MiG study) showed a strong association between the level of glycaemia achieved and pregnancy outcomes, such that the authors commented that lower glycaemic targets may be necessary. We do need RCTs of tight versus less tight management strategies with long-term follow-up of the babies. In the meantime, the recommendations of the 5th International Workshop are the best we have and seem appropriate.[22] (Table 3)

Table 3: Recommended glucose targets[17]

	Fasting	1 hr post-prandial	2 hr
ADA	105	155	130
ADIPS	100	145	125
CDA	95	140	120
5th International workshop conference on GDM	96	140	120

Abbreviations: ADA, American Diabetes Association; ADIPS, Australian Diabetes in Pregnancy Society; CDA, Canadian Diabetes Association.

Maternal and Fetal Risks

Glucose travels freely from the mother to the fetus, but maternal insulin does not. Thus, untreated hyperglycemia exposes the fetus to higher concentrations of glucose than normal, forcing the fetus to increase its own insulin production. Unfortunately, excess insulin produced by the fetus results in macrosomia, either from excessive fat deposition or as a direct growth effect of insulin. Mean maternal plasma glucose levels and fetal blood insulin levels are strongly associated with neonatal birth weight. Maternal glycemia during third trimester and prepregnancy body mass index are independent predictors of birth weight in pregnancies complicated by GDM. The occurrence of GDM imparts significant and long-lasting health risks on mother and baby (Table 4). Fetal programming in utero increases the risk of obesity and obesity-related complications in children of mothers with diabetes.[23]

Monitoring

Close monitoring and treatment of GDM are important to the long-term health of a pregnant woman and her baby. As mentioned above, The fifth International Workshop-Conference on Gestational Diabetes recommended the following blood glucose concentrations: fasting plasma glucose of 90 to 99 mg/dL, 1-hour postprandial plasma glucose less than 140 mg/dL, and 2-hour postprandial plasma glucose less than 120 to 127 mg/dL. Baseline and interval hemoglobin A1c levels during treatment are helpful, particularly in women who have fasting hyperglycemia.

Most women with GDM on diet treatment alone monitor capillary blood glucose levels 4 times a day (fasting blood glucose once a day and postprandial blood glucose thrice a day); women on drug therapy often monitor 4 to 6 times a day and include preprandial values.

Diet and Exercise

The initial treatment for GDM continues to be diet and exercise. Generally, a 1900- to 2400-kcal/d diet with carbohydrate restriction to 35% to 40% of calories is prescribed, calculated on ideal prepregnancy body weight and using complex and high-fiber carbohydrates. The assistance of a trained dietician is ideal for tailoring dietary needs for each woman. Dietary therapy delays pharmacologic therapy. Moses and colleagues[11] used a low-glycemic diet as treatment for GDM and in a prospective fashion showed that a low-glycemic diet decreased the need and timing for insulin. Most women lose weight during the initial weeks of dietary therapy but then resume modest weight gain. Insufficient dietary calories can be judged by excessive hunger, excessive weight loss, or persistent ketonuria.

If exercise is not contraindicated because of other obstetric complications of pregnancy, it can improve glycemic control in any type of diabetes. Women with GDM should be asked to walk 1 to 2 miles at least 3 times a week, if possible (Table 4).

Pharmacologic Therapy

Insulin

Pharmacologic therapy is most commonly instituted once diet and exercise have failed as evidenced

Table 4: Guidelines of the ACOG for exercise during pregnancy[24]

Exercise recommended in pregnancy	Exercise to be avoided in pregnancy
Walking Jogging/running Aerobic dance Swimming Cycling Dancing	Skiing Horseback riding Ice hockey Soccer Basketball Scuba diving
Intensity of exercise • 60%–90% of maximal heart rate • 50%–85% of either maximal oxygen uptake or heart rate reserve	
Duration and frequency • 30 minutes a day (in absence of either medical or obstetric complications)	

by abnormality in more than half of self-monitored glucose values or an abnormal value in those women tested weekly. Traditionally, insulin has been the drug of choice because of its safety in pregnancy, lack of significant transplacental passage, and history of use. Most women can be treated as outpatients. The recommended initial insulin dose for pregnancy is based on maternal weight and can be calculated by the following guidelines to determine total daily insulin needs: 0.7 U/kg actual body weight in the first trimester, 0.8 U/kg actual body weight in the second trimester, and 1.0 U/kg actual body weight in the third trimester. However, because women with GDM have varying degrees of severity, in practice, insulin is started at 0.7 U/kg actual body weight to prevent hypoglycemia at home. Clinical judgment and experience assist in the selection of the starting dose of insulin. Once the total daily insulin dose is calculated, two-thirds of the daily dose is given before breakfast, divided into two-thirds neutral protamine hagedorn (NPH) insulin and one-third regular insulin, and the remaining one-third of the daily dose is divided into half regular insulin before dinner and half NPH insulin at bedtime. To control postprandial hyperglycemia, short-acting or rapid acting insulin can be used, but is best dosed with each meal in place of the twice-daily regular insulin.[25]

For many years, fast-acting (regular) insulin, and intermediate-acting (isophane) insulin have been the preferred insulins for the treatment of GDM. Human insulin does not normally cross the placenta, though antibody bound animal insulin has been reported to do so. However, it has been shown by Jovanovic that it is maternal glucose control, rather than maternal anti-insulin antibody levels which influence birth weight. Human insulin is considered safe in pregnancy as years of experience has not suggested an increase in fetal complications as a consequence of its use.

There is now increasing evidence that the newer rapid acting insulin analogs lispro and aspart are also safe in pregnancy, and indeed, they are commonly used. No increase in pregnancy complications have been found in observational studies where lispro or aspart were used, in either women with GDM or pre-existing diabetes. With respect to GDM, there have been several small randomized studies comparing the use of rapid acting insulin analogues with regular insulin. They have all demonstrated that the rapid acting analogues are as effective as regular insulin in the treatment of GDM, with comparable, if not favorable, outcomes. Lispro & Aspart have been already approved by US FDA as class B drug for its use in pregnancy. As yet there have been no reports of the use of glulisine in pregnancy.

Long acting analogue, Levemir has been recently approved by USA FDA for its use in pregnancy as class B drug.[26] There are papers available in favour of use of glargine in pregnancy, but it, has not been approved yet.

Role of Oral Antidiabetic Agent

In the twenty-first century, oral hypoglycemic agents have been included in the armamentarium of treatment modalities for GDM Earlier concerns with use of these agents in pregnancy were the unknown risk of teratogenicity and neonatal hypoglycemia caused by transplacental passage. In 2000, Langer and colleagues published a small but landmark study[27] describing the use of glyburide for treatment of GDM. Women from 11 to 33 weeks of gestation with GDM were randomized to treatment with glyburide or insulin. There were no significant differences between the insulin treated group (201

women) and the glyburide group (203 women) in demographics and other characteristics, blood glucose concentrations, or neonatal outcomes. Glyburide was started at 2.5 mg in the morning and increased weekly to a maximum of 10 mg twice a day. The investigators concluded that glyburide is a clinically effective alternative to insulin therapy. In a retrospective study, Jacobson and colleagues[28] compared women with GDM treated with glyburide with those treated with insulin and noted that women in the glyburide group were more likely to achieve mean fasting and postprandial glucose goals and had newborns with similar weights and that the newborns were less likely to be admitted to the neonatal intensive care unit. The glyburide group had a higher rate of preeclampsia and need for phototherapy treatment of their newborns. In a different report, these investigators noted a somewhat higher risk of neonatal hypoglycemia with glyburide therapy,[29] but neonatal hypoglycemia may have been related to the higher rate of macrosomic infants in the group studied.

Glyburide does not seem to cross the placenta and may actually be actively transported from fetal to maternal circulations. However, other investigator have noted that the umbilical cord/maternal plasma ratio of glyburide is 0.7 +_0.4, suggesting transfer across the placenta and no active transport back. Failures of glyburide treatment can be predicted. Kahn and colleagues[30] reviewed 95 women with GDM in their diabetes clinic who were treated with glyburide. Of the 95 women, 19% failed glyburide treatment. Failures were more likely in women diagnosed early in pregnancy, of older age and higher parity, and with higher fasting glucose levels, reflecting reduced beta-cell function and reduced capacity to respond to insulin secretagogues. These factors should be considered with counseling or initiating glyburide therapy. Glyburide therapy alone is not likely to achieve optimal blood sugar control if the fasting glucose level is greater than 140 mg/dL and may not even achieve optimal control if fasting glucose level is between 120 to 140 mg/dL. Use of glyburide is not without pitfalls. Some practitioners and women have begun to believe that diabetes is not a critical complication of pregnancy because it can be taken care of with a pill. Thus, laxity in diet and compliance may occur more often. Experience with glyburide use in the first trimester, during embryogenesis, is limited, and safety in later trimesters should not automatically be extended to the early first trimester. Furthermore, glyburide may not be the ideal oral hypoglycemic agent for pregnancy. Its absorption and steady state and associated insulin secretion do not mimic the in vivo state. The ideal oral hypoglycemic agent for use in pregnancy is one that is not teratogenic, does not cross the placenta, and exerts its peak effect quickly after ingestion, mimicking in vivo insulin secretion and designed to be taken before each meal.

Metformin has been studied recently for treatment of GDM, because women often present to the obstetrician already pregnant and on metformin for treatment of polycystic ovarian syndrome, infertility, or metabolic syndrome. Rowan and colleagues[31] performed a randomized controlled trial of metformin versus insulin for treatment of GDM. A total of 363 women were assigned to metformin; 92.6% continued metformin until delivery, but 46.3% required supplemental insulin to achieve euglycemia. Neonatal outcomes were similar in each group, and women preferred metformin treatment even if insulin was added. In a randomized, controlled study, Moore and colleagues[32] compared the use of metformin with that of glyburide for the treatment of women with GDM. If glycemic control was achieved, women treated with metformin were comparable with women treated with glyburide in outcomes studied. However, failure of metformin therapy was 2.1 times higher than failure of glyburide therapy. Of the metformin group, 34.7% of women eventually required insulin, but only 16% of the glyburide group required insulin. The investigators speculated that ethnic differences may influence success of metformin.Until more information is obtained regarding safety and efficacy of metformin use in pregnancy, the best approach is to not use metformin for treatment of GDM. If a woman is already on metformin for other reasons, it is best to discontinue its use and perform diabetes screening at the appropriate time as indicated by risk factors or universal screening. Women on metformin for treatment of type 2 diabetes are best changed to insulin if unexpected pregnancy occurs.

Role of Other Oral Drugs

There is one study which randomized women with GDM to treatment with insulin, glyburide, or acarbose.[33] Forty two percent of the acarbose subjects failed to achieve adequate glycemic control and ultimately required insulin therapy. Furthermore, the high frequency of gastrointestinal side effects experienced by people with type 2 diabetes suggests

that any future role of acarbose, even if subsequent studies confirm safety, will be limited. There are no studies using glitazones in pregnancy.

Antenatal and Intrapartum Management

Once GDM is diagnosed, the pregnant woman should be seen at least every 1 to 2 weeks, more frequently if other complications ensue. Frequency and timing of antenatal testing in women with GDM is controversial. Generally, women on diet control who do not have macrosomic infants can wait until 40 weeks for antenatal testing; their risk of stillbirth is not substantially higher than the general population. It is prudent to manage women who are noncompliant, require pharmacologic therapy, have macrosomic or growth-restricted fetuses, or have other pregnancy complications similar to those women with preexisting diabetes and initiate antenatal testing. Close assessment of symptoms, blood pressure, and proteinuria to diagnose preeclampsia is of paramount importance. The timing and mode of delivery of women with GDM is also controversial given the lack of sufficient data to support a specific recommendation. There is no evidence to support delivery before 40 weeks of gestation. However, some investigators have found a higher incidence of shoulder dystocia by waiting for delivery until after 40 gestational weeks. Induction of labor at 39 gestational weeks in women with good metabolic control should not require documentation of fetal lung maturity by amniocentesis. Documentation of fetal lung maturity is prudent if delivery is electively planned earlier without other obstetric indications.

Women with GDM requiring pharmacologic therapy are best managed with intravenous insulin drips and glucose monitoring protocols during labor similar to women with pregestational diabetes. Women with very mild GDM may not require insulin therapy but should have blood glucose assessment during labor.

In light of the somewhat poor prediction of macrosomia by ultrasonography and the higher rate of shoulder dystocia in GDM infants when compared with non-GDM infants of comparable size, a fetal weight cutoff for vaginal delivery has not been easy to establish. The current recommendation is to offer women with GDM whose estimated fetal weight is 4500 g or greater elective cesarean to prevent shoulder dystocia. In those women whose fetal weight ranges from 4000 to 4500 g, clinical pelvimetry and other obstetric factors should assist in the decision to offer cesarean section.[34]

Postpartum Management

Many women who are diagnosed with type 2 diabetes are classified first as having GDM, even though they really have undiagnosed pregestational diabetes; these women continue to be diabetic in the postpartum period. Women with GDM should have a fasting or random blood sugar level test in the immediate postpartum period to identify undiagnosed type 2 diabetes. There is epidemiologic evidence that about 15% to 50% of women with GDM develop diabetes or impaired glucose tolerance well after pregnancy. A 75-g glucose, 2-hour glucose tolerance test should be performed at or around the time of the routine postpartum visit. The frequency of subsequent testing for detection of glucose intolerance or type 2 diabetes ranges from annually to triannually. The American Diabetes Association recommends glucose tolerance testing at least once every 3 years,[35] even though more frequent testing might be appropriate if further pregnancies are contemplated.

It is not surprising that there is marked variability in the proportion of women with GDM who are screened postpartum as well as in the type of screening used. Ferrara and colleagues[36] showed that between 1995 and 2006, the proportion of women in their study who were screened postpartum increased from 20.7% (95% confidence interval [CI], 17.8–23.5) to 53.8% (95% CI, 51.3–56.3). Independent predictors of successful postpartum screening in their study were women who were older, of Asian or Hispanic ethnicity, better educated, and diagnosed with GDM earlier in gestation. Obese women and women of low parity were less likely to have postpartum screening.

There are considerable data to support that weight loss and use of metformin or thiazolidinediones can prevent or delay progression of glucose intolerance and type 2 diabetes. Dietary modifications and treatment of periodontal disease may also prevent glucose intolerance. Additional research and specific clinical guidelines for women with history of GDM will allow interventional strategies to prevent or delay the onset of type 2 diabetes.

Role of Diabetes Educator - Diabetes Educator can play an important role in the management of diabetes during pregnancy.

- Preliminary Pre-conception counseling can be done by educator. They may discuss about withdrawal of oral antidiabetic drugs and importance of contraception before achieving

preconception glycemic targets (FBG < 90mg% and 2 hr PPBG < 120 mg%). Educator may discuss about role of insulin for achieving the target blood glucose before conception.

- Assessment of micro and macroangiopathy can be suggested before patient plans her pregnancy.
- Diabetes Educator is expected to spread the awareness about the myth that "Diabetic women cannot attain pregnancy"; about importance of blood glucose monitoring & control during pregnancy; dietary precautions during pregnancy & post-partum period.
- Importance of Post-partum follow-up can be explained to GDM women and her family members. They may be taught to follow healthy & disciplined life style to avoid obesity and diabetes in future.
- Diabetes Educator can also teach the lifestyle modification norms to offspring of diabetic mother, which may have its impact towards prevention of diabetes in these children in their adult life.

Summary and conclusions

Gestational diabetes is a common disorder which in the majority of cases, should initially be managed by dietary measures. These include a restriction in fat and simple carbohydrate intake, regular distribution of meals, carbohydrate foods favoring those with low glycemic index, and caloric restriction for those who are obese. Moderate physical activity should be encouraged. Fasting and post-prandial glucose testing is necessary for monitoring and guidance of therapy.

Where dietary measures are inadequate to achieve glycemic targets, insulin should be introduced. Insulin is still the mainstay of pharmacological treatment of GDM, and this is ideally administered in a basal bolus regimen. The rapid acting analogs lispro and aspart are considered safe, Levemir, a long acting analague has recently been approved by FDA USA for its use in pregnancy. There are few papers available favouring use of glargine in pregnancy but FDA USA has not approved it yet for pregnancy. Whilst there are studies demonstrating short-term safety of glyburide and metformin during pregnancy, it is suggested that they be reserved for situations where implementation of insulin therapy is impractical or not possible. After all, we know that insulin therapy is safe and usually effective. ACHOIS has shown that it is acceptable to the majority of women. By eschewing insulin, doctors may actually be succumbing to their own perceived fear of injections, rather than providing the best therapy to the patient. Based on our current information, insulin is still the best option, with the least potential for long-term risk to the mother and child.[17]

With good medical and obstetric care, the risks to the pregnancy should be minimal. However, a woman with GDM is a woman at high risk of future diabetes. Therefore after the pregnancy, healthy lifestyle measures should be encouraged to minimize the likelihood of developing diabetes, and regular screening for diabetes should be undertaken.

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Dietary Antioxidants and Diabetes

Salome Benjamin and *Sukhada Bhatte*

Abstract

Oxidative stress is considered to be a marker of pathogenesis of diabetes and diabetes related complications. With pharmacologic treatment alone being expensive, antioxidants are viewed as possible therapeutic adjuncts to tackle oxidative stress and eventually ameliorate diabetes related complications. The scope of this review is to search literature and derive the therapeutic dose recommendations from existing randomized clinical trials in humans. For the purpose of this review vitamins like vitamin E, vitamin C, lycopene and amino acid L-Arginine, Omega-3 fatty acids and trace elements like zinc (Zn), selenium (Se), chromium (Cr) and Vanadium (Va) will evaluated for their role in prevention and amelioration of diabetes and diabetes related complications. Several studies speculate supplementation of these vitamins and minerals along with anti-diabetic drugs to reduce oxidative stress and delay diabetes related complications. However, our review suggests that antioxidant supplementation has no specific benefit on the metabolic control in people with diabetes but may show effect on HbA1c suggesting a role in long term management in clinical trials. But there is scarcity of randomized clinical trials with conclusive results to confirm this. Our review also recognized that people with diabetes may have a deficiency of these vitamins and trace elements and hence, supplementation may be required to treat these deficiencies. Whether deficiency of these vitamins and trace elements leads to accelerated damage due to oxidative stress or deficiency is a result of oxidative stress in itself is unclear and needs to be explored. Furthermore, supplementation studies especially with vitamin E, Cr and Zn in huge dosages may have adverse effects and this aspect has not been extensively studied. Certain crucial aspects of supplementation studies such as comparison of source of antioxidants used viz. natural or synthetic, their bioavailability and effect of combined use needs to be extensively studied before deriving recommended therapeutic doses for antioxidant vitamins and minerals in treatment or amelioration of diabetes and diabetes related complications. Hence, an appropriate randomized clinical trial with exclusive and in combination supplementation of these vitamins and trace elements, as an adjunct to pharmacologic treatment needs to be studied in large number of population. With westernization of culture, Indian diets are particularly becoming deficient in vitamins and minerals and probable intervention in this area to prevent baseline deficiency may prove worthwhile. Nonetheless, these vitamins and trace elements may play a crucial role in preventing diabetes in people with insulin resistance or prediabetes before pharmacologic treatment has been initiated. Further studies in this area are warranted.

Keywords

- Dietary antioxidants and diabetes
- Oxidative stress and diabetes
- Vitamins and trace elements as antioxidants
- Vitamin E, Vitamin C, Lycopene, L-Arginine
- Zinc, Selenium, Chromium, Vanadium
- Omega-3 fatty acids, EPA, DHA and ALA

Methods

For the purpose of this literature review, PubMed, electronic peer reviewed journals on diabetes, metabolism, nutrition and dietetics, review articles, books, editorial correspondence, position statement of organisations were researched using combination of keywords like 'role of antioxidants in insulin resistance', 'insulin resistance and oxidative stress', 'oxidative stress as a pathogenesis of diabetes', 'antioxidants and diabetes, 'trace elements and diabetes' and 'vitamins and diabetes'. The scope of this literature review is to study vitamins and trace elements related to diabetes such as vitamin E, vitamin C, Lycopene and L-Arginine, zinc (Zn), Chromium (Cr), Selenium (Se) and Vanadium (Va). These searches were mainly restricted from year 2002 to 2012 i.e. the past ten years; however, certain

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relevant studies up to 1999 were also included for relevant data. Studies included in the review were mainly focused on papers published on therapeutic role of vitamins and trace elements in treatment and prevention of diabetes. Since diabetes is an inflammatory process leading to oxidative stress, papers focusing on role of trace elements in oxidative stress were also reviewed.

PubMed search for antioxidants and diabetes alone for the period of last 10 years 2002 to 2012 yielded 3827 research articles conducted particularly in humans. Animal studies were excluded. Studies focusing on role of antioxidants in diabetes, oxidative stress and role of vitamins and trace elements as antioxidants were scrutinised for significant data and included in the literature review. The scope of this review is to critically appraise literature relevant to the topic and comment on possible therapeutic use and dosage mechanisms.

LITERATURE REVIEW

Diabetes

Diabetes is a chronic disorder characterized by elevated levels of circulating blood glucose due to absolute or relative deficiency in insulin secretion and/or action and defect in carbohydrate, protein and fat metabolism.[1, 2] India has reached an alarming number of 61.3 million people with diabetes[3] and the prevalence is rapidly increasing in both urban and rural areas. Prevalence of diabetes in India is about 5-15% in urban population, 4-6 % in semi-urban and 2-5% in rural population.[4]

With rapidly improving socioeconomic status in India, there has been a rapid reduction in physical activity and quick adoption of unhealthy behaviours such as consumption of energy dense foods, increased exposure to risk factors such as processed foods, smoking and alcohol.[5] The Indian diets are becoming specifically deficient in vitamins, minerals and antioxidants due to adoption of western eating habits. Such behavioural risk factors are associated with metabolic and/or physiologic changes such as high blood pressure, increased prevalence of obesity, high blood sugars and deranged lipid profiles. According to the World Health Statistics 2012, diabetes directly accounts for 3.5% deaths due to Non communicable diseases.[4] An early detection followed by an early dietary and lifestyle intervention can assure 80% prevention of diabetes and diabetes related complications.[3]

Abdominal obesity, excess body fat percentage, increased subcutaneous intra-abdominal fat and deposition of fat at ectopic sites such as liver and muscle is a characteristic feature of an adult in urban India. About30-65% of adults in urban India are either overweight or obese or have abdominal obesity. Hence, Indians are predisposed to develop insulin resistance and cardiovascular risk factors at a lower BMI,[6] and therefore, early intervention is the necessary to prevent diabetes and diabetes related complications. An early dietary intervention to tackle this growing epidemic at a primitive stage may play a big role in prevention of metabolic disorders in India.

Insulin therapy and oral hypoglycaemic drugs have been effective in treatment of diabetes and related complications. However, the direct annual cost of diabetes care is INR 7158/- and the direct annual cost of hospitalization due to diabetes related complications is more than double to the average cost of diabetes care. This is unaffording for majority of people within lower income groups.[37] With expensive pharmacologic agents being used for management of diabetes and insulin resistance the need for newer and less expensive potential therapies arises especially for the vast majority of the population who cannot afford these medications.[7] Therefore, along with appropriate medications, diet and lifestyle changes and adjuncts to pharmacotherapy such as antioxidant therapy may play a significant role in management of chronic diseases like diabetes and cardiovascular disease.[8] Improvement of antioxidant status of individuals with obesity or/and insulin resistance and long term dietary antioxidant therapy can be considered as a potential adjunct to reduce the economic and social burden to prevent or manage diabetes and diabetes related complications.

Oxidative Stress

The role of oxidative stress in chronic disorders especially diabetes has been of great interest in the past decade. Oxidative molecules or free reactive species are produced as an immune response to foreign bodies such as medications, pollution, processed foods and even stress, hence, acting as a double edge sword and thus, posing a oxidative risk to the human host.[1] Oxidative stress is defined as excess prooxidants and reduced concentration of antioxidants leading to potential cellular damage.[9] Oxidative stress has a significant contribution to the onset and progression of diabetes and diabetes

related complications. Diabetes is a disease leading to metabolic derangement and hence, it depletes the body of cellular antoxidant defense mechanism [10] such as plasma antioxidants like catalase, superoxide dismutase, glutathione and glutathione peroxidase. [1] Hyperglycemia initiates a cascade of events causing damage of cellular proteins and cell surface markers leading to oxidative stress.[11] The role of oxidative stress in the pathogenesis of this multifaceted metabolic disorder has provoked the use of antioxidants as a complimentary therapeutic approach.[12]

Antioxidants

According to the Institute of Medicine, antioxidants have ability to significantly decrease the adverse effects of free reactive species such as reactive oxygen species and reactive nitrogen species on normal physiologic functions in humans.[9] In healthy individuals, antioxidant supply can be accomplished with a balanced diet with 3 servings of vegetables and 2 servings of fruits. However, deficiency may result due to inadequate dietary intake, intestinal disease or accelerated metabolic conditions like diabetes.[13]

The body combats oxidative stress using endogenous antioxidant enzymes and dietary antioxidants such as β-carotene, ascorbic acid, lycopene and vitamin E. Newer nutrient molecules, vitamins and minerals are viewed for their ability to scavenge free reactive species. Type 2 diabetes is characterized by obesity, dyslipidemia and cardiovascular events and is preceded by prediabetes or insulin resistance, giving potential avenue for early intervention and prevention of frank disease. Though diet and lifestyle is the primary option for prevention, often pharmacologic interventions are also required due to compliance issues. Hence, adjuncts such as dietary antioxidants which have relatively lesser side effects should be considered as a treatment option.[14]

Vitamin E

Meta-analysis study[15] which reviewed 14 vitamin E and vitamin C intervention studies found that there was no significant decrease in fasting blood glucose or insulin concentrations. However, HbA1c concentrations significantly decreased after vitamin E supplementation of 600mg/day for two months. Previous studies have shown some concern on prolonged supplementation of Vitamin E in high dosage and hence, long terms clinical trials in the perspective of diabetes management are required to establish safe dosage recommendations. Also, vitamin E (alpha-tocopherol) alone in doses of 400 units is of questionable value, and larger doses may cause intracranial hemorrhage or interact negatively with lipid-lowering drugs. Also, it is not recommended for use in patients who have bleeding disorders or are on anticoagulants.[13]

Vitamin C

Like Vitamin E, Vitamin C also does not have a significant effect on fasting blood glucose levels and insulin concentrations.[15] However, A 6 week vitamin C supplementation study with a dose of 1000mg/day suggested that vitamin C helps reduce fasting and post prandial oxidative stress and may help in preventing diabetes related complications. [16] But, this study was conducted with 30 subjects and hence a study with more number of subjects is needed to establish its benefits. People with diabetes may lose vitamin C due to polyuria and may require supplementation of 200 mg in non smokers and 250 mg in smokers.[13]

Lycopene

Lycopene is most abundant carotenoid in human diet and plasma amongst other carotenoids which denotes its probable role in antioxidant network in human body.[17] The exact mechanism of action of lycopene is unknown and needs to be studied further. However, due to its large number of conjugated double bonds, it is said to have potent free reactive species scavenging activity.[18] The Third National Health and Nutrition Examination Survey (NHANES III) stated that plasma lycopene levels reduced linearly with glucose tolerance status from pre-diabetic to diabetic state and is also associated with levels of insulin resistance.[19] Lycopene improves total antioxidant concentration by reducing uptake of ox-LDL by macrophage and foam cell formation. Therefore, it has a role in decreasing the risk of cardiovascular events especially in people with diabetes.[20]

L-Arginine

L-arginine is the substrate for the enzyme nitric oxide synthase (NOS) which is associated with production of nitric oxide (NO), a molecule responsible for development of atherosclerosis.[11] Hyperglycaemia and oxidative stress are characteristic features of diabetes which lead to endothelial dysfunction leading to increased production of free radical

species by vascular endothelium. L-Arginine is indicated to increase endothelial NO production and lowering free radical formation. A two month supplementation study,[14] found that L-arginine (3 x 2 g/day) supplementation had no effect on fasting blood sugars or H_{bA1c}. However, it showed significant increase in total antioxidant status (TAS) and NO concentration proposing an indirect antioxidant effect.[1] Further clinical trials with respect to dosage recommendations in humans, and its long term effect on chronic supplementation of L-Arginine in people with pre-diabetes or diabetes needs to be studied.

Omega-3 Fatty Acids

Omega-3 fatty acids especially Eicosapentaenoic acid (EPA) and Docosahexaenoic Acid (DHA) have shown promising results in treatment and prevention of obesity.[21] and may have a beneficial effect in prevention of diabetes. EPA and DHA or Alpha-linolenic acid (ALA) are considered as essential fatty acids and act as potent antioxidants. Supplementation with EPA plus DHA has not shown any significant effect on prevention of diabetes, however, ALA may be associated modestly with lower risk.[22] However, Certain other studies suggest that DHA may be more effective than EPA in prevention of insulin resistance. Purified EPA reduced insulin resistance in some but not in other normal weight or obese individuals.[12] This was probably due to health status of the participants, macronutrient, fatty acid, and antioxidant nutrient composition of basal diet, amount, duration, and fatty acid composition of omega-3 fatty acids, and methods used to assess insulin resistance. They observed that moderate amounts of omega-3 fatty acids did not improve or deteriorate metabolic glucose control in type 2 diabetics. In addition to this finding, the large scale prospective study viz., Women Health study found that higher intake of omega-3 fatty acids (≥ 0.20 g omega-3/d or ≥ 2 servings of fish/d) increased the risk of type 2 diabetes.[22] Furthermore, higher consumption of omega-3 fatty acids did not reduce the risk of type 2 diabetes.[21] In fact, higher intakes may increase the risk of developing diabetes. This is quite contradictory to the cardiovascular health benefits of omega-3 fatty acids. Hence, evaluation of omega-3 fatty acids in relation to prevention or treatment of type 2 diabetes to better understand their role in antioxidant therapy.

A DHA supplementation study (3g/day) concluded that lipocentric markers of insulin resistance such as LDL and ratio of TG/HDL-C are more responsive than glucentric markers such as postprandial insulin and glucose concentrations. Hence, further investigations in the role of DHA in prediabetes are essential.[23] It is difficult to comment on the whether omega-3 fatty acids have a role in prevention of treatment of diabetes due to such nonconclusive and conflicting data. Large scale randomized clinical trials are required to establish the use of omega-3 fatty acids in therapeutic doses for treatment and prevention of diabetes.

Trace Elements

Trace elements such as magnesium, zinc, selenium and vanadium may have a significant role to improve metabolic profiles in prediabetes and diabetes. The deficiency of these trace elements and suggested adjunct therapy to pharmacologic management of diabetes suggests a possible therapeutic potential. The possible mechanisms of these trace elements are: activation of insulin receptor signalling (chromium), antioxidant properties (selenium, zinc) or inhibition of phosphatases (vanadium) which indicates its importance in glucose homeostasis.[24] A randomized, double-blind, placebo-controlled clinical trial in 75 people with type 2 diabetes for 4 months, suggested that combined supplementation with minerals and vitamins such as zinc (20 mg), magnesium (250 mg), vitamin C (200 mg) and E (100 mg); along with vitamin B_1 (10 mg), B_2 (10 mg), B_6 (10 mg), biotin (200 µg), B_{12} (10 µg) and folic acid (1 mg) may ameliorate diabetic neuropathy symptoms (25) and may have role in amerlioration of other diabetes related complications.

Zinc

Zinc is an essential micronutrient, playing a role in proper functioning of various enzymes, about 300 cellular processes such as DNA and protein synthesis and intracellular signalling. It is also a very potent antioxidant. The pancreas is a secretory tissue with unusual zinc requirement, suggesting its role in pancreatic secretions.[26] It plays a significant role in insulin resistance and diabetes due to its ability to stabilize insulin hexamers, role in pancreatic storage of insulin and oxidative stress. Lower Zn plasma levels were not linked with glycaemic status or duration of disease in people with type 2 diabetes. However, it was found to be related to coronary artery disease and mortality in people with type 2 diabetes.[24]

Zinc is a potent antioxidant which competes with iron and copper for its action at specific sites and also binds

to SH group in proteins protecting them from oxidation. In a study conducted in women, high intake of zinc was found to be associated with slightly lower risk of type 2 diabetes. However, further prospective studies are warranted to understand the possible mechanism. It would be advisable to study association of type 2 diabetes/ insulin resistance with supplemental zinc and zinc from food sources separately as former is more bioavailable than latter.[25]

Selenium

Selenium another trace element found to have a crucial role in diabetes is also acts as an antioxidant in the form of selenoproteins such as glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases. Selenium is well absorbed from the diet especially in its organic form and therefore, selenium deficiency is rare. However, low selenium levels are reported in people with diabetes along with oxidative stress. Although in vitro studies have affirmed that selenium has potential antioxidant and anti-inflammatory effects, its therapeutic use to prevent or ameliorate diabetes and diabetes related complications requires human clinical trials to establish the correct recommended dosage, duration and form of selenium supplementation.[24] Prospective studies have shown benefit of higher selenium status in certain cancers, however, findings suggest that supplementation may only be beneficial in people with deficiency or inadequate intake. In fact, supplementation of selenium in people with adequate intake may increase their risk of type 2 diabetes.[27]

Chromium

Chromium has a significant role in metabolism of glucose and insulin and its severe deficiency is associated with impaired glucose tolerance, fasting hyperglycaemia and deranged lipid profile. When establishing requirements of chromium, one needs to account for its low availability from foods, increased requirement during physiologic conditions and most importantly release of chromium under stress conditions.[28] The safe and adequate daily intake of Cr was considered to be in the range 50-200 mg. However, now 30 mg/d seems a newly admitted value. Large scale clinical trials would be required to establish its role in amelioration of diabetes related complications. Chromium has no beneficial effect in healthy individuals who are not chromium deficient and therefore, assessing the chromium status of the individual is necessary before supplementing them with chromium as it could be toxic in high doses.[24]

Chromium is proven to alleviate insulin resistance, but, the molecular mechanisms are yet not clear.[29] Chromium is said to decrease insulin resistance by decreasing TNFα, resistin, interleukin-6, CRP and also by increasing vitamin C or adiponectin. In addition, to its effect on glucose and insulin metabolism, it is also said to reduce triglycerides.[24]

Vanadium

Vanadium (Va) is found to be insulin mimetic in in vitro studies and has been said to possess anti-diabetic properties. Certain studies however, found that Va potentiate insulin action and hence, has showing poor effects with insulin resistant and normoglycaemic subjects. Most of the human supplementation studies with Va in people with diabetes have been short term and with fewer subjects. Therefore, further studies are warranted to decide whether Va supplementation is actually beneficial and to derive the recommended therapeutic dosage.[24]

Comparison of Dietary Antioxidants Vs Pharmacologic Preparations

The American Heart Association has time and again suggested consumption of a balanced diet with antioxidant rich fruits and vegetables and due to lack of randomized clinical controlled trials no recommendations were made with regards to antioxidant supplements.[12,22] We also need to study in detail the role of these antioxidant molecules such as vitamin C, vitamin E, carotenoids and selenium beyond their role in traditionally deficiency diseases.[30] Nevertheless, the studies conducted so far are not consistent in the source of antioxidant used i.e. natural or synthetic, and do not guarantee the benefits of antioxidant supplementation (from whichever source) to prevent or ameliorate chronic diseases in a healthy individual with no deficiency of these molecules. Pharmacologic preparations are often either in excess of the dosage recommendations or not enough and the combination with other vitamins, minerals and antioxidants may make their bioavailibility questionable. Therefore, we have summarized dosages and the bioavailibility of antioxidants from dietary sources and pharmacologic preparations in Table 1.

Table 1

Summary of dietary antioxidants and their availibility from pharmacologic preparations:

Antioxidant	RDA	Dose recommendations	Toxic effects	Bioavailibility	Comments
1. Vitamin E	• For both men and women 15 mg (35 µmol)/day of α-tocopherol • Tolerable Upper Intake Level (UL) for adults is 1,000 mg (2,325 µmol)/ day of any form of supplemental α-tocopherol (30)	• 600 mg/day for 2 months in people with diabtes has beneficial effect n Hb_{A1c}(15) • Benefits of Alpha-tocopherol above 400 U is questionable (13)	• Larger doses may cause intracranial hemorrhage or interact negatively with lipid-lowering drugs. • Also, it is not recommended for use in patients who have bleeding disorders or are on anticoagulants. (13)	• Naturally occuring form (RRR-) and the other three synthetic 2R-stereoisomer forms *(RSR-, RRS-*, and *RSS-)* of α-tocopherol determine RDA • Other naturally occuring forms β–, γ–, and δ-tocopherols and the tocotrienols, though absored are not converted to α-tocopherol and hence does not account for RDA of vitamin E. (30)	• Overt deficiency is uncommon except in people wit h inherited disorders (30) • Benefits of vitamin E upplementaion in large doses either through dietray sources or harmacological preparations needs to studied in randomized clinical trials.
2. Vitamin C	• 40 mg/day (31) • RDA is 90 mg/ day for men and 75 mg/day for women (30) • Tolerable Upper Intake Level (UL) for adults is 2 g/ day (30)	• 1000mg/day suggested that vitamin C helps reduce fasting and post prandial oxidative stress (34, 19)	• Large doses may cause osmotic diarrhea and gastrointestinal disturbances.	• 70 to 90 % usual dietary intakes of vitamin C (30 to 180 mg/ day) is absorbed & however, absorption falls to about 50 % or less with increasing doses above 1 g/day. • The bioavailabilities of the vitamin from foods and supplements are not significantly different (30) However, natural sources would provide other health benefits like fibre, other micronutrients and antioxidants	• upplementation may be suggested in people with lesser intake of foods rich in vitamin C. • People with diabetes may lose vitamin C due to polyuria (13) and hence, may benefit from upplementation.
3. Lycopene	Not known	• 10 mg/d for 2 months helps prevents long term diabetic complication such as cardiovascular disease (2) • 1,2 and 4 mg/kg body weight has antinociceptive activity and	• None known	• *Cis*-isomers of lycopene are commonly found in the serum (30) and natural sources such as tomato juice has seen used in supplementation studies.Also, lycipene	• Lycopene improves total antioxidant concentration and may be important in using in combination with other antioxidants.

Antioxidant	RDA	Dose recommendations	Toxic effects	Bioavailibility	Comments
		potential to attenuate diabetic neuropathic pain (18)		increases with processing of natural sources.	
4. L-Arginine	• Not known	• 6 g/day supplementation had no effect on fasting blood sugars or HbA1c. But significantly increases TAS and NO concentration proposing an indirect antioxidant effect. (1)	• None known	• Not extensively studied	• Role of arginine in prevention of diabetes needs to be studied in detail
5. Omega- 3 Fatty Acids	• Not known	• A DHA supplementation study (3g/ day) benefits lipocentric markers of insulin resistance more responsive than glucentric markers (32)	• dose-related effect on bleeding time although abnormal bleeding as a result of fish oil supplementation has not been documented (16) • Dose dependant gastrointestinal disturbances also seen. (31)	• Bioavailability differs a lot among different pharmaceutical preparations and depensd on its concentrations. • Also, dietary sources may not have enough omega-3-fatty acids due to contamination of the dietary sources	Large scale randomized clinical trials are required to establish the use of omega-3 fatty acids in therapeutic doses for treatment and prevention of diabetes.
6. Zinc	• 12 mg/d (males) & 10 mg/d (females (33)	• Normal intake is 7-12 mg/day (33)	• High zinc intake can cause nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches	• All foodgrains are good sources of zinc. Like iron, zinc is lost on milling and processing of the grains and also, zinc bioavailability decreases with phytate rich diets. • Also, supplemental zinc is more bioavailable than zinc from food sources (25)	Zinc may have adverse effects in acute or chronic suppkementation and hence, proper evaulation of zinc status and its role in diabetes prevention needs to be studied further
7. Selenium	• 26 μγ/d for adult females and 36 μγ/d for adult males (33)	• 9-80 μγ Se requirements have been suggested	• Daily intakes above 700 μγ/d or acute consumption of	• Major dietary sources of selenium are cereals and	• Supplemen-ntation may only be beneficial in

Antioxidant	RDA	Dose recommendations	Toxic effects	Bioavailibility	Comments
		based on balance studies (33)	1-7 mg Se/kg/d results in toxicity in humans. • Dermatitis, depression and brittle finger nails are some of non specific symptoms of poisoning (33)	grians and the bioavailability from common foods is roughly 70-90%	people with deficiency or inadequate intake. • Role of Se in prevention and management of diabetes needs to be studied in a dose dependant manner.
8. Chromium	• 33 μγ Cr / d. (33)	• safe and adequate daily intake of Cr was considered to be in the range 50-200 mg. • However, now 30 mg/d seems a newly admitted value. (24)	• Not known	• When establishing requirements of chromium, one needs to account for its low availability from foods, increased requirement during physiologic conditions and most importantly release of chromium under stress conditions. (28)	• Cr supplementation reversed symptoms of glucose intolerance and insulin requirement. Hence, randomized clinical trials are warranted
9. Vanadium	• Not known	• Not established	• Not known	• Not extensively studied	• Further studies are warranted to decide whether Va supplementation is actually beneficial and to derive the recommended therapeutic dosage. (24)

Discussion

Vitamins and trace elements have been indicated to use in prevention, treatment and amelioration of diabetes and diabetes related complications. However, this review points out the need for conclusive randomized clinical trials to establish its recommended dosage and therapeutic implications. Most till date antioxidant vitamin studies have been heterogeneous and with no conclusive dosage recommendations. This deters therapeutic usage of these vitamins and trace elements in management and/or amelioration of diabetes and diabetes related complications. Majority of these studies have recognized that antioxidants can decrease free reactive species or oxidation end products and improve endothelial function, with an unclear role of antioxidants in improving metabolic control of these patients. Therefore, this evidence is insufficient to support high dosage of antioxidants in prevention and treatment of diabetes and diabetes related complications.[30]

The evaluation of these research papers suggests following benefits of these vitamins and trace elements:

- Vitamin E at a dose of 600 U/ day for two months showed a decrease in HbA1c with no significant benefit on fasting and post prandial oxidative stress. However, supplementation above 400 U should be used with caution

- Vitamin C at a dose of 1000 mg/day for 6 weeks helps reduce fasting and post prandial oxidative stress and may have a role in prevention of diabetes related complications
- Lycopene improves total antioxidant concentration and may be important in using in combination with other antioxidants.
- L-Arginine has no effect on fasting blood sugars or HbA1c but is said to increase total antioxidant status and NO concentrations
- Purified EPA may have a role in reducing insulin resistance and DHA has a probably role in improving prediabetes state. Studies suggest high dose of omega-3 fatty acid supplementation may in fact increase the risk of type 2 diabetes. Further studies are required to decide the recommended use of omega-3 fatty acids to prevent diabetes and diabetes related complications.
- Low zinc levels were not related to the glycaemic status but may have a role decreasing coronary artery disease and mortality in people with type 2 diabetes. However, increased intake of zinc may be associated with low risk of type 2 diabetes.
- Selenium was found to be low in people with diabetes and supplementation in people with adequate intake may increase the risk of diabetes
- Chromium is said to alleviate insulin resistance.
- Vanadium is said to be insulin mimetic but its exact role in antioxidant therapy needs to be explored

Micronutrient and vitamin antioxidants are said to interact with each other in the biochemical chain and to combat with free reactive species and a high dose supplementation with a single micronutrient or vitamin may offset the antioxidant-prooxidant balance causing potential risks. Hence, it is crucial to study the synergistic or antagonistic effect of these vitamins and trace elements.[25]

The current data clearly, suggests that trace element supplementation may not be beneficial in prediabetes or diabetes if the individual does not present trace element deficiency. There are possibilities that these trace elements in combination or along with other pharmacologic agents or antioxidants may have some value in therapeutic use.[24] Research in the area of effect of combining trace elements with other trace elements and antioxidant agents in treatment/ prevention of diabetes are needed. The vital question whether trace element supplementation is required to treat the condition or simply correct the trace element deficiency remains unanswered. This aspect needs to be studied further. Antioxidant status of an individual may also have an implication on understanding the pathophysiology and progression of diabetes or insulin resistance related disease process.

Further studies may be warranted with use of biomarkers to understand the effect of environmental prooxidant exposures and dietary antioxidant intake on prevention or amelioration of diabetes and diabetes related complications. To be effective a biomarker needs to be specific and should provide qualitative as well as quantitative values of antioxidant status.[9] This could be expensive and may have implications on its practical use. Nonetheless, it is necessary to understand parameters relevant to antioxidant status and oxidative stress to determine the selection of antioxidant, therapeutic dosage and duration of antioxidant intervention. It is important to remember that oxidative stress is an imbalance of oxidative molecules and antioxidants.

Conclusion

Diabetes is a metabolic disorder characterized by hyperglycaemia and oxidative stress which has a crucial role in development of micro and macro vascular complications. Though, in vitro studies suggest that use of antioxidants may help diminish the effect of oxidative stress and therefore, delay diabetes related complications. However, evidence suggests that antioxidant supplementation has no specific benefit on the metabolic control in people with diabetes. Studies have recognized that people with diabetes essentially have a deficit of these vitamins and trace elements and therefore supplementation is recommended only in individuals who are identified to be deficient in these vitamins and trace minerals. Furthermore, supplementation of these antioxidant vitamins, amino acids, fatty acids and trace minerals in huge dosages has not been extensively studied. We also need to discover the synergistic and antagonistic effect of these supplemental vitamins and minerals with the innate antioxidant molecules present in human plasma. Understanding the role of these antioxidant molecules in protection against diabetes may provide us with effective measures to lessen the economic burden of the disease. Additionally, study of use of dietary sources of these antioxidants versus commercial

formula, their bioavailability, effect of combined use and side effects of long term use is necessitated before deriving recommended therapeutic doses for antioxidant vitamins and minerals in treatment or amelioration of diabetes and diabetes related complications.

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Abbreviations

Zn	:	Zinc
Cr	:	Chromium
Se	:	Selenium
Va	:	Vanadium
NHANES III	:	The Third National Health and Nutrition Examination Survey
LDL	:	Low density lipoprotein
TAS	:	Total Antioxidant Status
NO	:	Nitric oxide
EPA	:	Eicosapentaenoic Acid
DHA	:	Docosahexaenoic Acid
ALA	:	Alpha-Linolenic Acid
TG	:	Triglyceride
HDL-C	:	High Density Lipoprotein-C

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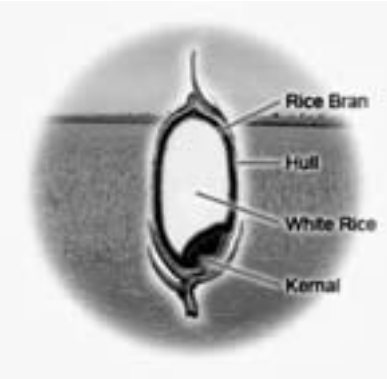
Rice Bran Oil: Most Friendly Oil for Indian Hearts

Sweety Das

The ever growing demand and soaring prices of edible oils can be controlled by tapping the sources of unconventional oils, rice bran oil being one of them.

What is Rice bran oil (RBO)?

Rice Bran Oil (RBO) is an unique edible oil produced from rice bran which is a by product of the Rice Milling Industry. The crude rice bran oil is extracted from the rice bran through the solvent extraction process using food-grade hexane as a solvent. The crude rice bran oil then undergoes a refining process to obtain the Refined Rice Bran Oil fit for human consumption.



Potential benefits of RBO

- RBO has a fatty acid composition similar to that of groundnut oil with an ideal fatty acid profile as suggested by the American Heart Association (AHA).
- A rich source of vitamin E complex, naturally occurring source of many other antioxidants such as Tocopherols, Tocotrienols, Gamma Oryzanol, Phytosterols, Polyphenols and Squalene and other micronutrients to help fight free radicals and combat the effects of aging.
- The components of rice bran oil give it an outstanding shelf life.
- The viscosity of RBO is very light and the flavor delicate. Foods cooked with it absorb up to 20% less oil. Less oil absorbed results in reduced calories, better, lighter tasting food and enhanced flavor and palatability making it more economical.
- Rice bran oil has a very high smoke (burn) point, making it perfect for deep frying, pan or stir frying and is a premium choice for the replacement of hydrogenated oil containing Trans fat now being used in deep fryers.
- RBO is hypoallergenic. For those who have intolerance to other cooking oils this is an excellent alternative.
- The actual cost of RBO is not significantly different than other high-grade vegetable oils on the market making it consumer-friendly.
- It creates fewer polymers than other oils meaning better flavor and easier clean-up.
- In addition to the above mentioned benefits, RBO was also found to decrease bone mineral loss caused due to hormonal imbalances in postmenopausal women.

Role of RBO for CVD health

It is estimated that up to 30% of deaths from coronary heart disease (CHD), which is one form of CVD, are due to unhealthy diets (National Heart Forum 2002). This implies that dietary changes could have a positive impact on the number of people affected by CVD, both in terms of death from the disease and disability as a result of the disease. There is good evidence that a reduction in the total amount of fat and in particular saturated fatty acids (SFA) like ghee, butter, margarine, coconut oil is paramount to improving CVD risk.

The beneficial role of RBO in hypercholesterolemia & hyperlipidemia has been proved by various human & animal studies. A significant reduction in the serum lipids (triglycerides, LDL, VLDL & TC) & lipid peroxides was reported in the healthy humans on RBO supplementation.

Current Guidelines for consumption of fat as recommended by AHA

- ***Saturated Fatty Acids***

Individuals should consume less than 10% of calories from saturated fatty acids. Based on scientific evidence, 10% is too high for heart health. AHA urges the Committee to consider revising the current recommendation to less than 7% of energy from saturated fats.

Sources: The main sources of saturated fat are from animal products like red meat and whole-milk dairy products, including cheese, sour cream, ice cream and butter. Other sources are vanaspati ghee, coconut oil, palm oil.

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- ***Trans Fatty Acids***

AHA recommends that Trans fat consumption be as low as possible, but no more than 1% of energy; this equates to a maximum of 3 grams per day based on a 2,000 calorie diet.

Sources: Major contributors to Trans fatty acid intake are baked goods such as doughnuts and pastry, deep fried foods such as fried chicken and french fried potatoes, and imitation cheese. Snack chips, cookies, and crackers often contain high amounts of trans fat as well.

- ***Omega-3 Fatty Acids***

Two servings per week of fatty fish like salmon, tuna, trout, herring and sardines are recommended. Intake of these omega-3 fatty acids has been associated with a decreased risk of cardiovascular disease.

- ***Comparison of physical & chemical RBO with other oils making it an ideal cooking oil***

Studies conducted in India & abroad on Groundnut Oil and Cottonseed Oil have proved beyond doubt that Rice Bran Oil has much better oxidation stability than these two oils due to its moderate level of naturally occurring saturated fatty acids, low linolenic acid content, higher oleic acid levels coupled with much higher natural anti-oxidants. A 1:1 blend of Cottonseed Oil and Rice Bran oil have been found to have significantly better oxidation stability indicating longer shelf-life. Also, RBO has two and a half times to five times more oxidation stability as compared to Groundnut Oil depending upon its Oryzanol content. Even the uptake in the fried food products has been reported to be less by 5 to 10% as compared to Groundnut Oil. A further advantage is its natural resistance to smoking at high frying temperatures.

Palm Oil no doubt is very stable oil for frying due to its very high levels of saturated fat & mono-unsaturated oleic acid content and very low levels of poly-unsaturated fat, but the saturated fats at the levels found in the Palm Oil are not considered good for human health.

Besides exhibiting excellent frying performance, Rice Bran Oil contributes a pleasant flavor to the fried food. These properties make it a premium choice for frying upscale products ranging from potato chips and similar snacks to chicken & fish with excellent taste and texture profiles. Rice bran oil is also superior salad, cooking, and frying oil which leaves no after taste. The high smoke point prevents fatty acid breakdown at high temperatures. Its light viscosity, allows less oil to be absorbed in cooking, reducing overall calories.

Olive Oil: High monounsaturated fat, able to lower cholesterol but deficient in polyunsaturated fat, which contains Essential Fatty Acids (EFA). EFA's are truly essential to life as every metabolic process in your body depends on them. A low smoke point makes it a poor choice for frying, and its heavy taste makes it undesirable in many baked goods. Traditionally a good salad oil.

Canola Oil: High monounsaturated fat with cholesterol lowering ability but there are concerns about the origin. "Canola oil" is a term coined by Canada to change the name of "rapeseed oil". The rapeseed plant contains erucic acid making it toxic and is used as an industrial lubricant. It has been genetically modified and hybrid to produce a low erucic acid version. Commonly hydrogenated, it is extensively used in the food industry because of its low price. The hybrid plant would be the best choice.

Peanut Oil: A good balanced oil. This oil has good cholesterol lowering ability and a high smoke point, making it good frying oil. It imparts a slightly earthy, nutty flavor. It lacks the anti-oxidants and micronutrients of Rice Bran Oil. A small percentage of people are allergic to nut oils.

Soybean Oil: This oil is a high poly fat. As recommended by the AHA your poly fat intake should be around 33% of your total fat intake. A high poly percentage is, an aid to tumors and cancer and should be carefully watched. Up to 80% of the oil consumed in the U.S.A. today comes from soybeans. Soybean oil is commonly hydrogenated and used in many processed foods.

Comparison of smoke point and balance of fats in some commonly used oils:

Oil Type	Smoke Point	Mono-Unsaturated Fat	Poly-Unsaturated Fat	Satu-rated Fat
Rice Bran Oil	490º	47%	33%	20%
Olive	360º	77%	9%	14%
Canola	450º	61%	33%	7%
Peanut	460º	48%	34%	18%
Soybean	440º	24%	61%	15%
Grape seed	485º	14%	77%	9%

Search for edible oil with ideal composition has resulted in the concept of blending of oils. Composition of the resultant oil blend is expected to exhibit more therapeutic benefits than the individual constituent oils.

Thus, it may be concluded that among the various unconventional oils, RBO is one of the most potential health oils that could be consumed for prevention as well as curation of the most commonly occurring degenerative diseases such as CVD, Hyperlipidemia, cancer etc.

Popular brands of RBO available in the market:

- **Ricela**
- **Saffola gold *(blend of RBO & Kardi oil)***
- **Saffola active *(blend of RBO & soyabean oil)***

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Quality of Dietary Fats And Oils : Its Role in Health and Disease

Sonal V. Modi

Introduction

The dietary fat available from different fats and oils in foods is digested, metabolized and absorbed variably in the body. In nature, both dietary fat as well as the lipids in the body are made up of basic units called fatty acids. These fatty acids are usually long chain chemical compounds made up of hydrogen and carbon and their chemical make up determines their ultimate fate and function in the body.

There are specific enzymes in the body which synthesise and breakdown these fatty acids. Mainly, the breakdown of fatty acids releases energy to perform the different functions of the human body.

Types of Dietary Fat

The fat which is added in the diet while cooking as cooking oil as well as at the table while dining is termed visible fat. This kind of fat is mainly found as butter, ghee, hydrogenated oils and all vegetable oils. On the other hand, dietary fat found naturally in foods is termed invisible fat. It may be obtained both from animal and plant sources. The animal source is from milk and milk products, poultry, fish, seafood and meat and the plant source is from cereals, pulses, millets, nuts and oilseeds and green leafy vegetables. Green leafy vegetables are also rich in certain fatty acids which are essential for the body eg. linoleic acid and alpha-linolenic acid. One has to be prudent and select the right quality of dietary fat in the diet. The invisible fat from plant sources (seeds, nuts, grains, greens) is a healthier option to the visible fat (processed or refined) and invisible fat of animal origin.

Composition and Metabolism of Dietary Fat

The dietary fats found ubiquitously in nature are quite complex. Their structural, physical and chemical existence ie. how they are naturally found in foods plays a crucial role in deciding its function in the body and use in cooking.

These fatty acids are found with a backbone of carbon atoms which are of different lengths. There is short chain (carbon 4-8), medium chain (carbon 10 -14) and yet another a long chain group (carbon 16 -22) of fatty acids.

Each group being slightly varied gets metabolised differently. The short chain and medium chain group are absorbed and transported more efficiently by the body. On the other hand, the long chain group takes an indirect and less efficient path of metabolism.

A unique group of substances called medium chain triglycerides originates from coconut oil and contains 8 to 10 carbon units .It is absorbed directly by the lymphatic system and hydrolysed more easily than classic triglycerides. These medium chain triglycerides are used widely in conditions of malabsorption and steatorrhea (fatty stools).

Properties of Dietary Fat

Nature has its unique design for all. The different fatty acids are part of this plan, with specific structure and layout which leads to their inherent quality specific role . Some of these aspects need to be delved into to enable one to fathom the function of these various products of nature.

Butter and ghee are hard substances at room temperature. Their short chain fatty acid make up bestows this property on them. The fats containing longer fatty acids are more fluid at room temperature. This length of the fatty acid chain decides their biological effect on blood lipids. The short chain fatty acids give the additional benefit of being anti-inflammatory in the body. They also increase production of leptin, a hormone which decreases food intake. Medium chain fatty acids and long chain fatty acids for example, coconut oil, palm oil (chemically name: lauric, myristic and palmitic acid) tend to raise the low density cholesterol. On the contrary, short chain fatty acids like ghee, butter do not seem to exert a detrimental effect on the blood lipids. Infact,

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one of the long chain fatty acid, stearic acid also does not affect the cholesterol levels adversely. Hence, the impact of all the short, medium and long chain fatty acids on the human body need to be re-examined.

The type of bonding the fatty acid displays greatly influences the quality of fat. As we know, saturated fat found in dairy, meat, poultry products and vegetable oil like coconut and palm oil contains zero double bonds. This fat is an undesirable fat for the body. In the sixties, a classic study called the 'seven countries study' established the fact that incidence of ischemic heart disease rose with an increased intake of SFA and dietary cholesterol. Infact, a minimal 100 mg increase in dietary cholesterol raised the total cholesterol by a drastic 12 mg %.

On the other hand, the monounsaturated fats with one double bond (found in olive, peanut and canola oil, nuts, avocado and olives) were found to reduce low density cholesterol and beneficially keep triglyceride and high-density cholesterol at par.

Whereas the polyunsaturated fats which contain two or more double bonds (found in corn, soyabean, safflower, sunflower oils and some varieties of fish) were found to reduce triglyceride and low-density cholesterol levels more effectively. But, was found to simultaneously reduce high-density cholesterol.

Interestingly, inspite of both the monounsaturated and polyunsaturated fats exerting positive effects on blood lipids, it is the former which maintains the high density cholesterol at the same level.

Type of Unsaturation

The type of unsaturation is important in determining the function of fatty acids. Two common groups known, are the omega-3 polyunsaturated fats eg. linolenic, eicosapentanoic, docosahexanoic acid and the omega-6 polyunsaturated fats eg. linoleic, arachidonic acid. The former group exerts a positive effect on blood lipids and anti-inflammatory response of the body. Omega-3 fats are found mainly in flaxseeds; nuts, especially walnuts; oily fish, for example pomfret, rohu, sardine, mackerel, Bombay duck. Omega-6 fats are found in mainly safflower oil, sunflower oil, soyabean oil, cottonseed oil. The advantages and disadvantages of omega-3 and omega-6 polyunsaturated fats and their impact on coronary heart disease has been discussed over the decades. Today, it is a known fact that the ratio needs to be optimal to produce a favorable effect on blood lipids. The benefit of these fats outweigh their drawbacks, yet they have to be included judiciously in the diet. The third group of fats, which are not produced in the body and available only from the diet and is called essential fatty acids eg. linoleic acid and linolenic acid.

Configuration of hydrogen atom:

The structural dimension to fatty acids is determined by the configuration of hydrogen atoms around the molecule. The 'cis' form is the natural form of fatty acid found ubiquitously in plants and animals. It maintains the integrity, fluidity and porosity of the cell membrane. Unfortunately, the process of hydrogenation converts this 'cis' form to a 'trans' form destroying functionality of the cell. This 'trans' form of fatty acid is responsible for unfavorably increasing triglycerides, low-density cholesterol and decreasing high-density cholesterol. This further accelerates the process of atherogenesis. The hydrogenation process causes the conversion of 'cis' to 'trans' fatty acid produces fatty acids with straighter chains than the natural unsaturated fatty acids also. Usually, hydrogenation is undertaken commercially to enhance product taste, stability and shelf-life. This detrimental 'trans' fat is found in commercially fried foods, baked goods and snacks, margarine and vegetable shortenings which is widely consumed by all. An awareness regarding these 'trans' fats on the food label is required to bring about a wave of change in the overconsumption of processed foods.

Comparatively, traditional fats are mainly obtained from natural whole foods, especially plant-based foods and unrefined natural oils. Nuts, a calorie-dense food generally containing high monounsaturated fats and polyunsaturated fats, is a rich source of the right type of fat, especially for vegetarians. It is a healthy alternative to high-fat containing processed foods and plays an important role in many weight reduction programs worldwide. For centuries, the use of unrefined oils was propogated. This is because unrefined oils preserve nutrients, antioxidants, have a low smoke point, are sensitive to light and prolonged heating. They possess a short shelf-life and their storage and packaging is important.

Processed fats are of two types, refined oils and partially-hydrogenated fats. Refined oils are odorless, bland, have a high smoke point, are stable at high temperature and hence possess a long shelf-life. Refining strips the oil of its antioxidants (carotenoids

and tocols). Also, the linoleic acid and linolenic acid it contains is unstable to oxygen and light. Additionally, the linolenic acid has the lowest melting point ie. 10°F, which is destroyed on processing.

Partially-hydrogenated fats undergo processing to improve texture, taste and shelf-life. It is responsible in generating 'trans' fatty acids and free radicals which in turn promote diabetes, cancer and ischemic heart disease . Infact, partially-hydrogenated fats are more harmful than refined oils.

Other Properties of Fats:

The cooking property and shelf-life of various fats and oils is extremely crucial for its appropriate use. Cooking oil has certain characteristics such as its flavor, texture, smoke point and price. Smoke point is the temperature at which any oil begins to smoke, discolor and decompose. Beyond this smoke point, the food burns and gives an unpleasant taste. Usually, unrefined oils have a lower smoke point than refined oils. Hence, oils with a high smoke point are ideal for cooking and frying, whereas oils with a low smoke point can be used for sautéing for short periods. Hence, unrefined oils should be used in the end-cycle of cooking. For example, sesame seed oil, extra-virgin olive oil, peanut oil , flaxseed oil can be used for boiling, steaming, light sauté and as a salad oil due to their low smoke points. On the other hand, butter, vegetable shortening, canola oil, soyabean oil, cottonseed oil, groundnut oil can be used for stir-frying, browning and deep frying due to a higher smoke point.

Summary

All types of dietary fats have their pros and cons. Disadvantages of dietary fat include atherogenesis, increased oxidative stress, increased eicosanoid production, increased carcinogenesis and thrombogenesis. In the present state day, a low fat diet (approximately 20-30% of calories) where fat is derived from varied sources appears appropriate. Saturated fats (with appropriate SCFA, LCFA) and MUFA oils need to be reassessed. Unrefined oils, omega-3 PUFA and the 'cis' form of oils offers a great advantage.

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INSULIN ANALOGUES
Where are they Needed Most?

Benny Negalur

Insulin was discovered in 1921 by Sir Fredrick Banting and Sir Charles Best which transformed the management of diabetes.

Insulin that was initially used initially was obtained by extraction and purification from the pancreas of cows called bovine insulin and from the pancreas of pigs called porcine insulin. These animal insulin's have slightly differently placed amino acids in their structural sequences e.g. beef insulin differs from human insulin by three amino acid whereas pork insulin differs by only one amino acid. These are in fact the first Natural Analogue Insulins.

Amino acid structure of human insulin

With the advent of recombinant DNA technology large scale production of human insulin was possible having the same amino acid sequence as insulin in the human pancreas. Insulin analogues were developed with recombinant DNA and protein engineering techniques in which the structure of the insulin molecule is modified in such a way as to change its pharmacokinetics without altering the biological effect. These are known as insuin analogues.

Normal insulin is present in the vial as hexamer. When injected in the subcutaneous space, it breaks up into diamers and monomers and then get absorbed. The rapid acting analogues, because of the structural modification exists in monomeric form and equally importantly

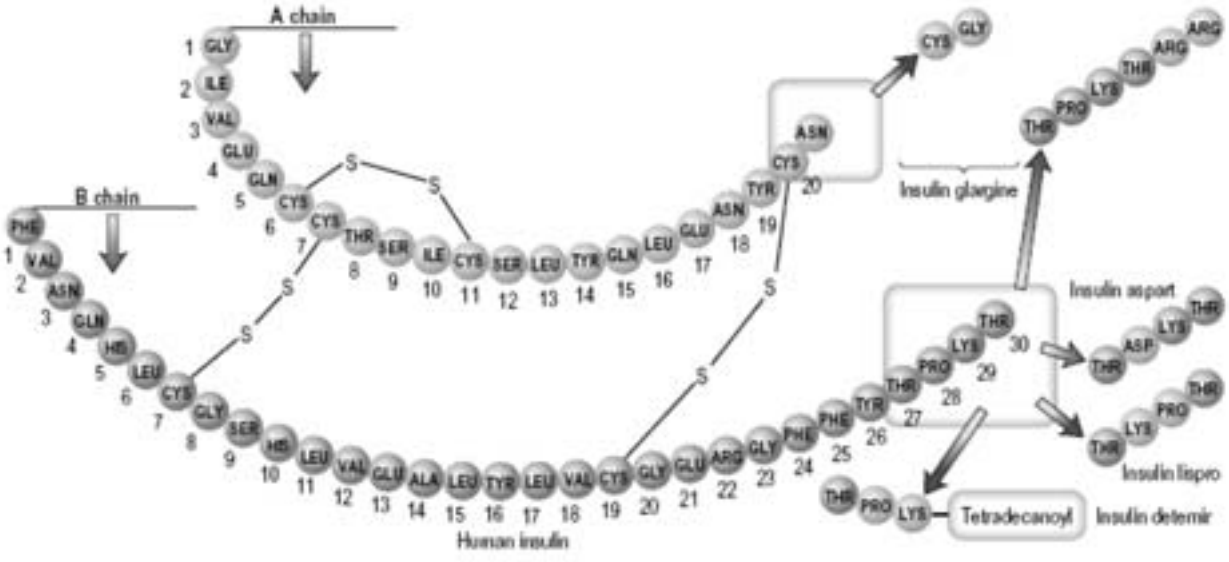
disappears from the circulation more rapidly than soluble insulin. So they offer more convenient and flexible insulin injection schedule.

Rapid acting Analogues were developed to mimic the normal mealtime insulin response. They have a faster onset of action, an earlier peak, and shorter duration of action than regular human insulin, so can be used before or just after a meal.

They are Insulin lispro, Insulin aspart and Insulin glulisine

Lispro is a rapid acting insulin analogue created by reversing the order of the amino acid proline and lysine in positions 28 and 29 of the B chain.

Aspart is a similar analogue created by replacing proline at position 28 of the B chain with the aspartic acid residue.



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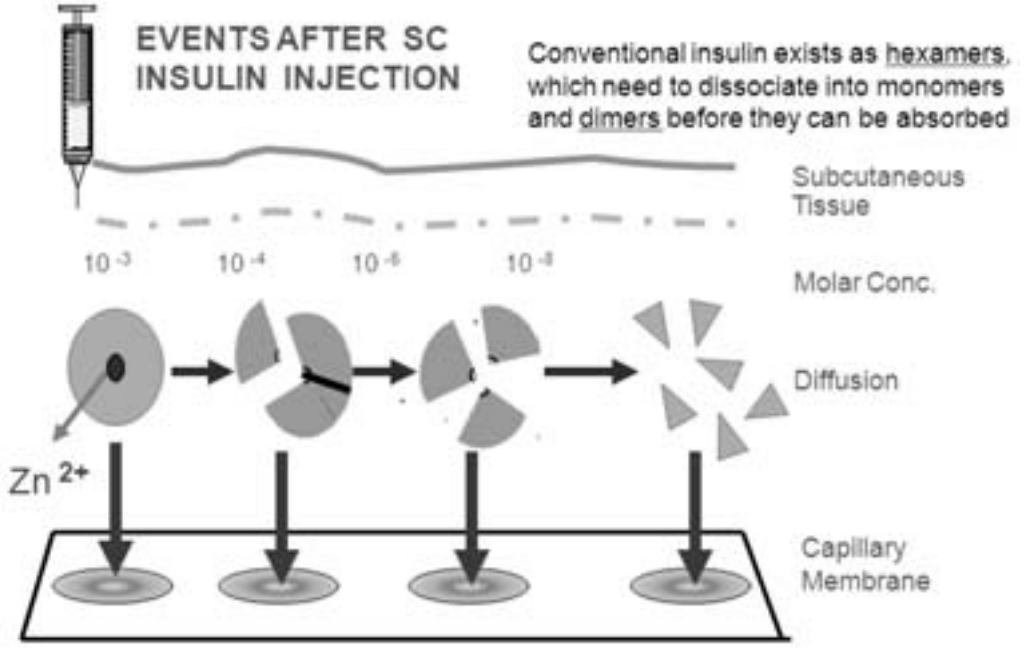
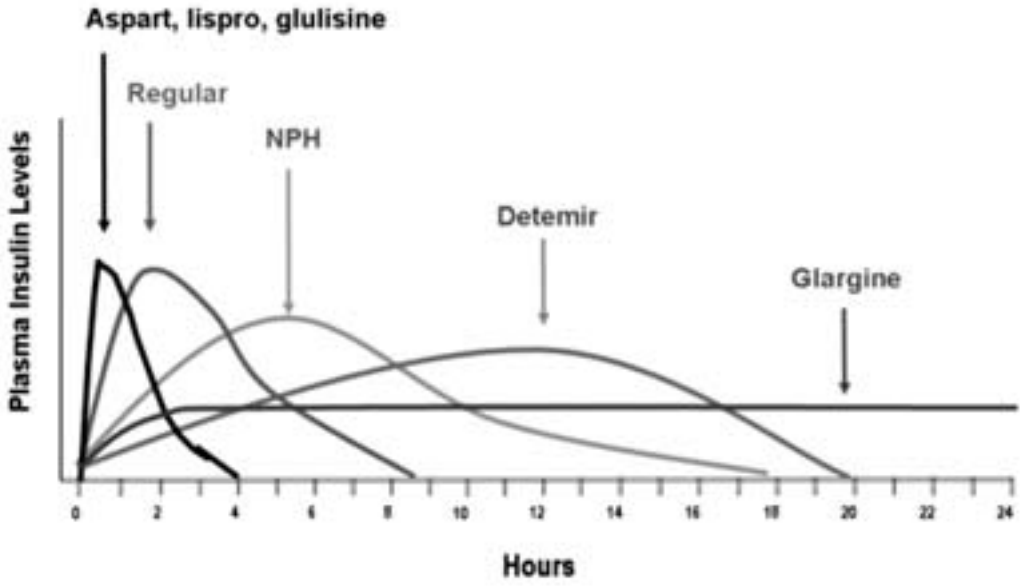


Insulin glulisine is a rapid-acting insulin analogue that differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid

LONG ACTING INSULIN ANALOGUES require only one daily injection, have a more prolonged action and achieve more predictable glycemic control. They are called basal insulins as they are taken to keep background glucose levels steady. They are peakless insulin.

Glargine Insulin- it is a long acting insulin created by replacing asparagine in position 21 of the A chain with a glycine residue and adding two anginines to the end of the B chain

Time Duration curves of various Insulins

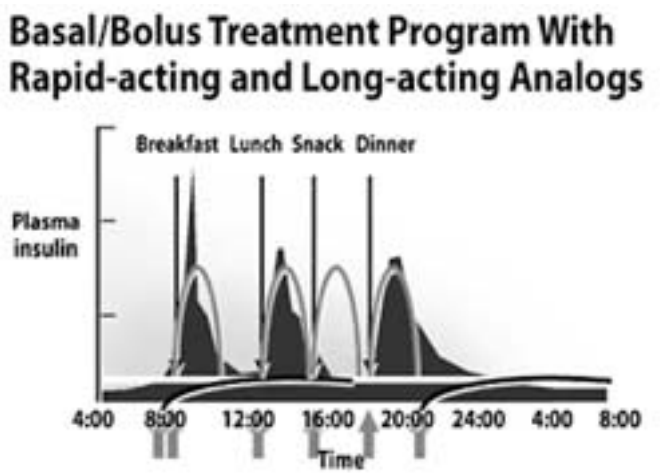


Detemir Insulin - Insulin detemir omits threonine in position 30 of the B chain and adds a fatty acyl chain to lysine in position B29.

Biphasic Insulins – Mixture of rapid and intermediate acting anaogues produces mixed analogues which have a rapid onset of action,followed by a basal supply, thus allowing administration closer to a meal. These premixed analogue insulins are generally administered twice daily and can used in either type of DM.

COMPARISON OF HUMAN INSULINS AND ANALOGUES

Insulin Prepatations	Onset of Action	Peak	Duration of Action
Lispro	5-15 minutes	30-75 minutes	2-4 hours
Aspart	5-15 minutes	1-2 hours	3-6 hours
Glulisine	5-20 minutes	1-2 hours	2-4 hours
Human Regular	30-60 minutes	2-3 hours	4-8 hours
Human NPH/Lente	1-2 hours	4-8 hours	10-16 hours
Glargine	30-60 minutes	peak less	~ 24 hours
Detemir	30-60 minutes	peak less	20-24 hours



WHERE ARE INSULIN ANALOGUES NEEDED MOST?

SHORT –ACTING ANALOGUES

They have advantages over regular insulins, they may be used as bolus therapy in the basal- bolus regimen especially when there is a need to control high prandial sugars. They are used to minimized the nocturnal hypoglycemia as they are more rapid acting compared to regular insulin and the effect wears off in about 2-3 hours. At times late interprandial hypoglycemia is a problem or there is a need to control blood glucose without snacks between meals when rapid acting analogs are preferred.They are indicated in renal failure when there are wide sugar fluctuations and hypoglycemia is more common. During illness or when there are episodes of vomiting rapid acting analogues can be given even after a meal as the meal size cannot be determined earlier. Rapid acting analogs are also safer in the elderly patients where hypoglycemia is more likely with routine therapy.During long hours of travel especially during air travel insulin analogue, can be taken after meals as frequency of meals increased or decreased depending upon time gained or time lost. However rapid acting insulin analogues have no advantage over regular insulins and are not required for use in intravenous insulin infusion in hospitalized or ICU patients .

Long-acting analogues:

They should only be used in T1DM when nocturnal hypoglycemia or morning hyperglycemia occur with NPH insulin or when rapid acting insulin analogues are being used for meal-time blood glucose control. Long acting analogues are recommended for T2DM patients as a single dose insulin who require assistance to administer insulin, have significant hypoglycemia or would otherwise need additional oral antidiabetic medications. Premixed insulin analogues should be considered in Type 2 DM,when hypoglycemia is a problem or blood glucose levels rise markedly after meals.

Drawbacks of Insulin Analogues:

Insulin analogues have limited efficacy and safety advantages over standard human insulin, they carry higher prescribing costs which limits cost effectiveness, and there is a lack of long term safety data. These issues should be considered carefully before commencing treatment with an insulin analogue.

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Secondary Diabetes: Drug Induced Diabetes

Niyati Likhite

Secondary diabetes mellitus refers to elevated blood sugar levels that develop in association with some known medical condition. This kind of diabetes occurs usually secondary to another primary disease or condition. The most common causes of secondary diabetes are pancreatic disorders, endocrine problems, drugs, chemicals agents or toxins and genetic mutations or syndromes.

Drug Induced Diabetes:

Drug induced diabetes can be defined as new development of hyperglycemic state that meets the definition of diabetes due to ingestion of a drug

Insulin secretion can be impaired by many drugs. These drugs may not cause diabetes by themselves, but they precipitate diabetes in individuals with preexisting insulin resistance and deficiency. Hormones like glucocorticoids, growth hormone, etc when in excess or when given as therapy, can impair the action of insulin. Toxins such as rat poison (Vacor) and specific drugs like pentamidine, steptozotocin can permanently destroy the beta-cells of the pancreas.

According to the mechanism of action, the diabetogenic drugs can be divided into following categories:

1) Drugs that causes diabetes by interfering with insulin production/ secretion

   e.g: Pentamidine, L-asparaginase, Phenytoin, Diazoxide, Phenothiazines, streptozotocin, Alloxan, Vacor

2) Drugs that cause diabetes by reducing the effectiveness of insulin, i.e. decreasing insulin sensitivity

   e.g: Steroids, β-agonists

3) Drugs that affect both insulin secretion and insulin sensitivity

   e.g: Thiazide diuretics, Immunosuppressants

4) Drugs that induce diabetes independent of insulin

   e.g: Nicotinic acid

Drugs that causes diabetes by interfering with insulin production/ secretion

Pentamidine: It is an anti-parasitic drug used in infection in HIV patients and some fungal infections. It can cause irreversible beta-cell damage, leading to loss of insulin secretion and resulting in diabetes. It initially causes hypoglycemia followed by β-cell destruction and impaired insulin release that leads to hyperglycemia.

L-asparaginase: it is an antineoplastic drug used in treatment of leukemia. It impairs the insulin biosynthesis by depleting asparagie molecule. Low levels of asparagine may inhibit the insulin production since the insulin molecule contains three asparagine residues. Diabetes resolves on withdrawal of this drug.

Phenytoin: It is used for treating seizure disorders. It blocks calcium ion channels in the pancreatic beta-cells, inhibiting insulin release resulting in hyperglycemia. It can resolve once the medicine is discontinued.

Diazoxide:

Diazoxide is a vasodilator commonly used in the past for control of malignant hypertension. It inhibits insulin secretion and has been used in the treatment of hypoglycemia. It acts on the pancreatic beta-cell and prevents insulin release. It is reversible upon discontinuing the drug.

Phenothiazines: It causes hyperglycemia by inhibiting insulin secretion. Large doses of chlorpromazine in the short term can inhibit insulin secretion and can induce hyperglycemia in both healthy persons and in patients with latent diabetes mellitus.

Streptozotocin: It is used as antibiotic and antineoplastic drug. The use of this compound in the treatment of malignant pancreatic islet cell tumors can cause severe hyperglycemia due to its effects on the β cells. It's effects damage β-cell membranes and

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cause breakage of DNA stands. This drug is mostly used for animal studies.

Alloxan: This drug is used as antineoplastic agent. It acts on both cell membrane and inside the cell. It inhibits glucose stimulated insulin release and inhibits glucokinase. This drug was the first known diabetogenic chemical agent.

Vacor: This drug is directly toxic to β-cells. Accidental or deliberate ingestion causes rapid death of the insulin producing islet β-cells. There are two phases to this process:

1) Insulin releases from dying cells which causes hypoglycemia
2) There could be complete insulin deficiency, which causes diabetes or diabetic ketoacidosis.

Drugs that cause diabetes by reducing the effectiveness of insulin, i.e. decreasing insulin sensitivity

Steroids:

It includes glucocorticoids, oral contraceptives and sex hormones.

Glucocorticoid – induced diabetes can be detected within hours of administration of pharmacologic doses of the steroid. It encourages breakdown of stored protein and fat which causes an increased stream of free fatty acids and branched amino acids to the liver. This increases hepatic glucose output. Hepatic glucose output is usually regulated by insulin, but the effect of insulin is diminished in the presence of steroids. Glucose uptake by fat and muscle is reduced due to insulin resistance and direct steroid effects. Hence, it increases average glucose concentration by decreasing insulin sensitivity.

Oral contraceptives – They are steroid combinations that increase average glucose concentrations by decreasing insulin sensitivity. Hyperglycemia is reversible on withdrawal of the pills. However in large epidemiologic studies, there is little evidence to link oral contraceptives and diabetes.

Sex Hormones – The effects of sex hormones on carbohydrate metabolism remain complex and controversial. Hormonal variations during the menstrual cycle and pregnancy may modify the results of oral glucose tolerance and insulin tolerance tests. Natural estrogens can improve glucose tolerance and enhance insulin sensitivity. Estrogen increases insulin binding in fat, liver and diaphragm plasma membranes. Progesterone may produce similar effects in the absence of estrogens, but progestins appear to antagonize the effects of estrogens when given in combination. Progesterone and progestogenic drugs may reduce the number or affinity of insulin receptors on cell-surface membranes.

Impaired glucose tolerance has been reported to be greater in users than in nonusers of the birth-control pill. The effects on glucose tolerance of the birth-control pill may be dose dependent and are usually reversible after discontinuation of the agent. The insulin resistance induced by oral contraceptive agents is associated with reduced peripheral tissue insulin sensitivity and may ameliorate with time. Early birth-control medication contained a much higher dose of estrogen, and these large doses may have contributed to glucose intolerance.Use of low-dose oral contraceptives may not significantly influence glucose tolerance

β-agonists: β-agonists mimic the effects of adrenergic members of the counterregulatory hormone system in response to hypoglycemia. It causes insulin resistance, diminished glucose utilization and increased glucose production. Stimulation of β- adrenergic receptors will increase the hepatic glucose output and diminish insulin sensitivity. Oral route is more diabetogenic than subcutaneous route. It is more deleterious in pregnancy.

Drugs that affect both insulin secretion and insulin sensitivity

Thiazide diuretics: They are used as a first line of therapy for treatment of hypertension. Thiazides have been implicated as a factor in inducing glucose intolerance in non-diabetics and diabetics in many studies. Higher doses are more likely to be associated with glucose intolerance. Glucose intolerance may develop after years of treatment. Relative risk of developing diabetes is more in males.

Diuretic-induced hyperglycemia may be due to decreased insulin secretion as a result of hypokalemia. The reduction in total body potassium correlates with a reduction in insulin secretion. Correction of low potassium can prevent the deterioration in glucose tolerance and may restore insulin sensitivity. Hence, it may be reversible on restoring normal potassium levels. A direct toxic effect on the pancreas has also been postulated.

Immunosuppressants:

Cyclosporine: Cyclosporine is a fungal metabolite used as an immunosuppressant to prevent the rejection of transplanted organs. The incidence of diabetes in previously non-diabetic renal transplant recipients who receive cyclosporine has been reported to be from 2% to 46%. However, cyclosporine is usually given in concert with glucocorticoids, which are diabetogenic of themselves and may have an additive or synergistic effect.

The mechanism of cyclosporine-associated diabetes is a combination of inhibition of pancreatic function and increased insulin resistance. Both insulin secretion and peripheral insulin action appears to be perturbed.

Of the currently available immunosuppressive agents, glucocorticoids and calcineurin inhibitors, tacrolimus and cyclosporine have been consistently associated with New Onset Diabetes after Transplantation (NODAT).

Drugs that induce diabetes independent of insulin

Nicotinic acid: It is an effective therapy for cholesterol problems. It is associated with increased levels of blood glucose levels in diabetics as well as in non-diabetics. The mechanism for nicotinic acid induced hyperglycemia includes increase in hepatic glucose output, enhanced glucose production secondary to rebound increase in flow of free fatty acids (FFA) to liver.

In conclusion, drug-induced diabetes occurs due to a variety of drugs. An underlying and often unsuspected abnormality in carbohydrate metabolism in the patient or a family history of diabetes greatly increases the risk for developing drug-induced diabetes. All the above mentioned drugs increases the risk in patients with abnormalities in plasma glucose. These drugs interfere with insulin secretion or utilization of insulin or both. Factors like dosage of drug, duration of drug intake, concomitant ingestion of other medication, severity of illness, nutritional state, alcohol intake and pancreatic islet cell reserve are responsible for increasing blood plasma glucose. In case of some of these drugs it can be treated by discontinuing the medication while for those drugs that cannot be avoided, with their known effects on carbohydrate metabolism, it becomes necessary to monitor the plasma glucose. Thus, in patients suffering from drug induced diabetes, treatment should be similar to that of patients with type 2 diabetes mellitus, but insulin is invariably required to obtain metabolic control. In addition, patient must receive comprehensive diabetic care along with diet and exercise plan. Among the common offenders are steroids, thaizide diuretics (like hydrochlorothiazide) and nicotinic acid. However, the effects with diuretics and nicotinic acid is mild and should not preclude the use of these effective drugs in diabetics (for control of hypertension and cholesterol).

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Bariatric Surgery

Shaival Chandalia

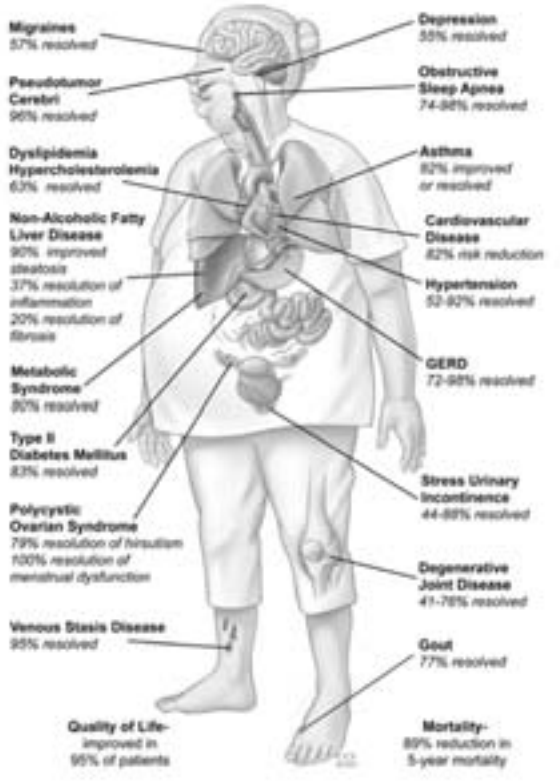
Obesity has increasingly become a public health menace of epidemic proportions. As infectious diseases decrease in frequency due to the progress made by modern science in terms of immunizations and antibiotics, non communicable diseases like obesity, diabetes and heart disease have come to the forefront. Also these diseases are interlinked. Obesity is fuelling the twin epidemic of type 2 diabetes in India and both are responsible for one of the highest incidences of heart disease in Indians compared to other ethnic groups.

Why is treatment of obesity important?

The problem with obesity is not merely a cosmetic one. It is true that obesity is associated with psychological problems, difficulties in adjustment and ostracisation by society. However, even more insidious is the fact that the risk of certain type of cancers increase in obese patients. The risk of type 2 diabetes, hypertension and heart disease also increases and this has already been alluded to. The association between type 2 diabetes and obesity deserves a special mention. Obesity is associated with a condition called insulin resistance. Insulin resistance implies that there is enough insulin circulating round in the blood but it is not able to act effectively because of resistance to its action at the level of the cell. This increase in fat in obese patients reduces the effectiveness of insulin and sooner or later results in type 2 diabetes.

Interestingly, the fat cell is now gaining primacy as an endocrine organ. It has been found recently that fat, far from being an inert organ for energy storage, is also an endocrine organ. It secretes various hormones which in turn affect various metabolic processes in the body. Extensive research is on to elucidate this new role of fat and it is hoped that this may offer key insights into the role of fat in health and disease.

Apart from increased risk of various non communicable diseases like heart disease and cancer, there are many mechanical sequalae of



carrying excess weight. Excess weight puts additional strain on the joints specially the weight bearing joints and may result in early degeneration of these joints (called osteoarthritis). This in turn results in a vicious cycle whereby the joint problem prevents these patients from exercising which leads to worsening obesity and this in turn leads to worsening of the joint problem. Aside from this, obesity is associated with a condition called obstructive sleep apnoea where in , the upper airways get blocked (due to the excess fat) during sleep resulting in the patient temporarily ceasing to breathe for a few seconds (during sleep). This is obviously harmful and needs to be treated. Similarly, the excess fat on the chest wall can restrict the lungs from taking a full breath causing a condition called obesity hypoventilation syndrome.

How does one measure obesity?

Traditionally obesity is measured by an index called

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the body mass index. The BMI (body mass index) is measured by taking the weight (in kg) and dividing it by the square of height (in m^2). Thus, this index serves to standardize obesity measurements among people of different heights so that it is comparable between different individuals. BMI between 25 to 30 kg/m^2 is considered overweight (mild obesity), and 30 to 40 obesity. BMI > 40 kg/m^2 is morbid obesity or severe obesity.

There are other measurements that one can do for obesity such as measuring the skin fold thickness using a pair of callipers. This offers additional useful information about the degree of obesity. However, BMI remains an important prognostic index, indicating the higher risk of dying (from various causes, some of which have been mentioned earlier) as the BMI increases.

What are the medications available to tackle obesity?

Obesity remains an area of extensive research today. It is a difficult problem and a dark area in modern medicine inspite of the extensive research going on. We are limited in our choices with regard to medications available to treat obesity. Currently there are two medications that are approved to treat obesity. These are sibutramine and orlistat.

Sibutramine is an appetite suppressant. It works on the central nervous system reducing appetite. It is a safe drug and produces a weight loss of 5 to 6 kg. Diet and exercise must continue with either of the 2 medications (sibutramine or orlistat) otherwise both these medications will be ineffectual. There was some concern that sibutramine can worsen high blood pressure or increase the pulse rate but recent studies have shown that it can be used safely in patients who are at a high risk for cardiovascular disease (like heart attacks or strokes).

Orlistat, the other medication that can be used is a fat blocker. Normally fat in the diet is broken by an enzyme called pancreatic lipase secreted by the pancreas. Orlistat blocks this enzyme so that the fat in the diet passes unabsorbed into the stools. This medication is safe, the major side effect being unpleasant gases or oily stools, specially on eating fat rich foods. Thus this drug can be unpleasant in social circles because of the aforementioned side effect. Since the drug is not absorbed, and works only in the gut, there are few if any systemic side effects. Orlistat produces a similar weight loss of 5-6 kg (as sibutramine).

Against this background, there has emerged a surgical treatment of obesity. With medications few and far between and long term difficulty in sustaining weight loss by diet, exercise and/or medications, a surgical approach to treatment of obesity has emerged. This is called bariatric surgery.

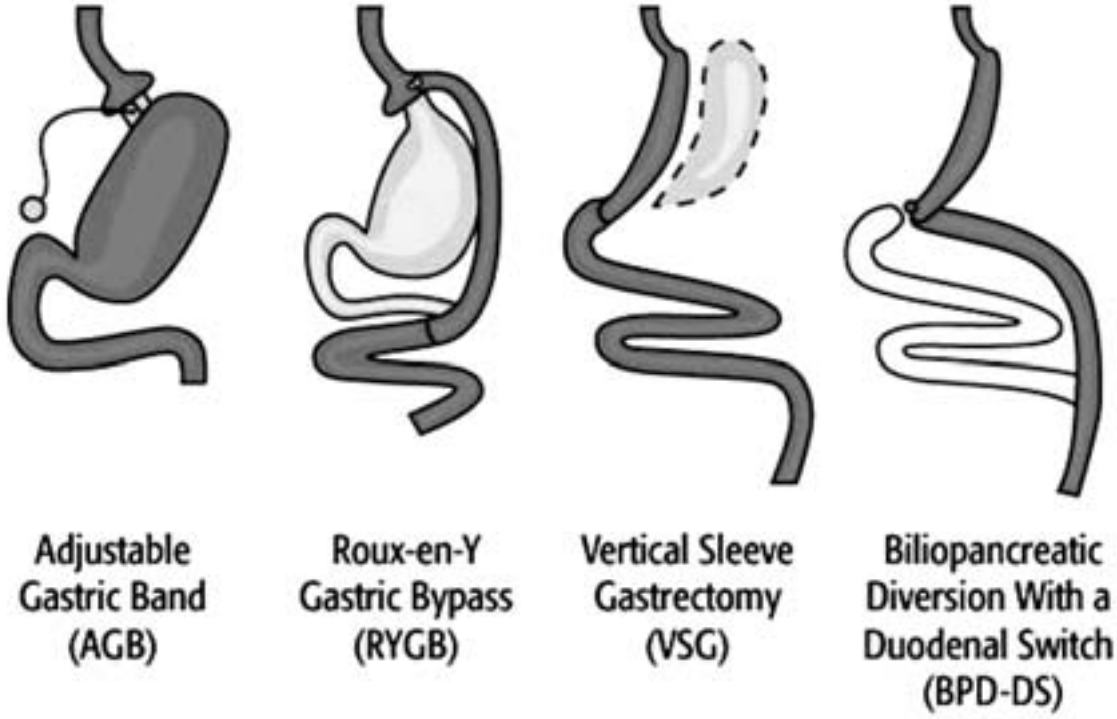
Bariatric Surgery

Bariatric Surgery includes all procedures which are done in order to treat obesity. Traditionally, these surgeries are restricted to severe obesity (morbid obesity – BMI > 40 kg/m^2) where the benefit versus risk ratio of surgery is overwhelmingly in favour of surgery. i.e. extremely obese patients have a much higher risk of dying from natural causes than the risks of undergoing surgery. Weight loss in such people is desirable at any cost.

As the severity of obesity becomes milder and milder, however, the risks of surgery (by no means inconsiderable) have to be weighed carefully against the benefits of weight loss. As expected in any new emerging modality of therapy, a great deal of ambiguity and controversy exists. Hopefully, with more studies and more and more evidence gathering this ambiguity will be clarified. At the moment, bariatric surgery is recommended unequivocally for those patients with a BMI > 40 kg/m^2 (as mentioned earlier) and those with a BMI > 35 kg/m^2 who suffer from various co-morbid conditions, i.e. associated conditions like uncontrolled hypertension, diabetes or obstructive sleep aphoea (among others). Bariatric surgery is not considered appropriate (at the moment) for patients with a BMI < 35 kg/m^2.

There is a school of thought, however, that the most effective treatment for diabetes mellitus is not a medication but bariatric surgery i.e. bariatric surgery can be performed even in patients with normal BMI and diabetes in order to cure diabetes. This however, is highly controversial and studies are needed in order to judge whether this approach has any benefit in the long term. As mentioned curlier, the risk of surgery have to be weighted carefully against the benefits of weight loss and/or metabolic control. Remember that there is a risk of dying from bariatric surgery of 0.1 – 1% depending on the specific procedure performed.

What are the principles of bariatric surgery?



Bariatric surgery works on two principles-a restrictive component and a malabsorptive component. The restrictive component implies that the size of the stomach is restricted by surgical means (in most cases the size of the stomach is reduced to form a pouch for food intake). This results in immediate satiety and restriction of food intake. The malabsorptive component implies that in certain types of bariatric surgery (like gastric bypass), the digestive portion of the gut (where food and food digesting enzymes are present) is bypassed to produce a degree of malabsorption i.e. all the food is not digested and absorbed, and passes though the gut and out of the body unabsorbed.

Types of bariatric surgery

There are many types and varieties of bariatric surgery but some deserve special mention. One is laparoscopic adjustable gastric banding and the second is gastric bypass. Laparoscopic adjustable gastric banding (LAGB) is the method by which the stomach size is restricted by placing a band over it using a telecope like device. The size of the band can be varied. This is a minimally invasive procedure and the risk of death in this procedure is minimal (0.1 %). However, the results of weight loss are significantly less than the other variety of bariatric surgery called Roux-en-y gastric bypass. Gastric bypass involves reducing the size of the stomach and also bypassing a part of the digestive tract producing malabsorption (as mentioned earlier). So this surgery includes a restrictive component and a malabsorptive component. The benefits with respect to weight loss are much better and more sustained compared to LAGB. However, the risk of death (mortality) during the procedure is higher at 0.5-1%. Of course in experienced hands, this figure may be much lower. Also the complications post surgery like deficiency of nutrients like vitamins and minerals (due to the malabsorption) are more as compared to LAGB.

Summary

Bariatric surgery is an exciting new branch of surgery which is much talked about today. In the severely obese patient, the surgery can significantly change the longevity and quality of life. As yet, there is no data to support using this modality of therapy in the mild or moderately obese and/or diabetic patient. The risks and benefits of bariatric surgery have to be carefully weighed against each other before proceeding with the surgery.

■

Stress Management in Diabetes

Niyati Likhite

Stress is your body's way of responding to any kind of demand. Stress results when something causes your body to behave as if it were under attack. Stress can be defined as any type of change that causes physical, emotional or psychological strain. However, not all types of stress are harmful or even negative. It can result from either good or bad experience. Sources of stress can be physical, like injury or illness or they can be mental like problems in your marriage, job, health or finances. Stress can complicate diabetes by distracting you from proper care or affecting blood glucose levels directly.

Types of Stress:

There are a few different types of stress that we encounter:

- **Eustress,** a type of stress that is fun and exciting, and keeps us vital. It is also known as positive or good stress.
- **Acute Stress,** a very short-term type of stress that can either be positive (eustress) or more distressing (what we normally think of when we think of 'stress'); this is the type of stress we most often encounter in day-to-day life. It is also known as fight-or-flight response. The most common symptoms are emotional distress , muscular problems ,stomach, gut and bowel problems , elevation in blood pressure, rapid heartbeat, sweaty palms, heart palpitations, dizziness, migraine headaches, cold hands or feet, shortness of breath, and chest pain. This kind of stress can crop up in anyone's life, and it is highly treatable and manageable.
- **Episodic Acute Stress,** where acute stress seems to run rampant and be a way of life, creating a life of relative chaos. The symptoms include persistent tension headaches, migraines, hypertension, chest pain, and heart disease. Treating episodic acute stress requires intervention on a number of levels, generally requiring professional help, which may take many months.
- **Chronic Stress,** the type of stress that seems never-ending and inescapable, like the stress of a bad marriage or an extremely taxing job. The symptoms of chronic stress includes headaches, increased susceptibility to colds and may precipitate more serious health problems like depression, diabetes, hair loss, obesity, hyperthyroidism, sexual dysfunction, tooth and gum disorder, ulcers and anxiety disorder.

Stress and Diabetes:

Stress, both physical and mental, can affect your blood sugar levels. When stress occurs, the body prepares to take action. This preparation is called fight-or –flight response. In this, levels of many hormones shoot up and their net effect is to make lot of stored energy which is in the form of glucose and fat, available to cells. But in diabetics, the fight-or-flight response doesn't work well, as insulin is not always available to allow the extra energy to enter the cells. Hence the glucose piles up in the blood.

Non-diabetics have compensatory mechanisms to keep blood sugar from swinging out of control but in diabetics such mechanisms are lacking or blunted. Stress hormones may alter blood glucose levels directly. In diabetes due to absolute lack of insulin such as type 1 diabetes or a relative lack of insulin such as type 2 diabetes, there is not enough insulin to cope up with these hormones and hence the blood sugar rises.

When the blood sugar levels are not controlled well, one is at higher risk of many health complications like blindness, kidney problems, nerve damage leading to foot numbness and hard to heal infections. Prolonged elevated blood sugar is also a predecessor to cardiovascular disease which increases the risk of heart attacks and strokes.

Managing stress in Diabetes:

Stress can affect your blood glucose level, so managing stress when you have diabetes, helps managing your blood glucose level. Stress plays a

This article is reproduced from Diabetes today, Vol 21, No 4;Oct- Dec, 2011 with permission. Ms Niyati Likhite, Dietician, Dr. Chandalia's Diabetes Endocrine Nutrition Management and Research Centre (DENMARC), Mumbai. Email Id: **niyatichitre@gmail.com**

major role in controlling blood sugar levels. People with diabetes should stay conscious of eating well and exercising regularly. They should check the blood glucose levels frequently when they are ill or under stress and should take lot of fluids, as not to get dehydrated.

Impact of stress on Diabetes:

1) People under stress may have increased appetite and land up eating more and exercising less. It also encourages cells in your abdomen to conserve fat that seriously raises your risk of a heart attack. Hence, reducing stress helps you stick to your eating and exercise goals, which in turn keeps your diabetes under control.
2) Many studies found that diabetics have elevated blood glucose levels when they are under stress, as the body releases stress hormones which sends glucose stores into blood to make energy available to your muscles, this results in higher blood glucose levels. These hormones also make your heartbeat and breathing speed up.
3) Stress contributes to insulin resistance. Stress hormones also make it difficult for the pancreas to secrete the insulin that is required to remove glucose from the blood.

Although you can't completely remove stress from your life, there are several ways you can reduce it and keep your diabetes under control.

- Fight your stress with a positive attitude, try to find something good in each important area of your life: work, family, friends and health.
- Always feel good about yourself. Don't expect more of yourself than you have or are able to give.
- Develop a simple plan of action for those stressful situations or problems that cannot be changed.
- Talk to someone about your stress, you can share it with your family or close friends who would be able to give you some support and insight. You can also approach a counselor or a psychologist.
- Take up exercise to reduce your stress. Benefits of exercise are well known in reducing stress, particularly for those with diabetes. Exercise gives you a feeling of well being and may relieve symptoms of stress.
- Take time to relax. Relaxation includes brief or quick relaxation like muscle relaxation, stress walk, deep breathing, meditation or visualization.
- Take care of your meal schedule as well the quantity and kind of food you eat. A regular meal schedule is crucial in reducing stress and controlling blood glucose. Fluctuating and skipping meals make it stressful for your body to naturally regulate and utilize nutrients. Try to focus on eating approximately the same time daily without skipping meals.
- Build up your immune system by taking precautions to avoid potential illnesses. Stress reduces your body's ability to fight infections and resist illness. Hence, reducing stress will keep your immune system strong which in turn helps you control your blood glucose levels.

Stress and Diet:

A well balanced healthy diet is crucial in preserving health and helping to reduce stress. Certain foods and drinks act as powerful stimulants to the body and hence are a direct cause of stress. These stimulants may have harmful in the long run. Here are some examples:

1) Caffeine

This is found in coffee, tea, chocolate, Coke, etc. It causes the release of adrenaline, thus increasing the level of stress. If consumed in moderation, coffee can increase your alertness and increase activity in the muscles, nervous system and heart. Consuming too much caffeine has the same effect as chronic stress. Reduce the consumption slowly over a period of time.

2) Alcohol

Alcohol is a major cause of stress. If taken in moderation, alcohol is a very useful drug. It has been shown to benefit the cardiovascular system. Most people drink alcohol as a way to reduce stress but actually it worsens it. Alcohol stimulates the secretion of adrenaline resulting in the problems such as nervous tension, irritability and insomnia. Excess alcohol will increase the fat deposits in the heart and decrease the immune function. Alcohol also limits the ability of the liver to remove toxins from the body. During stress, the body produces several toxins such as hormones. In the absence of its filtering by the liver, these toxins continue to circulate through the body resulting in serious damage. Alcohol and stress, in combination, are quite deadly.

3) Smoking

Many people have cigarettes for reducing stress. In short term, smoking seems to relieve stress. But in long term smoking is very harmful. Cigarette smoking is shown to be responsible for a variety of cancers, hypertension, respiratory illness and heart disease.

4) Sugar

Sugar has no essential nutrients. It provides a short-term boost of energy through the body. High sugar consumption puts a severe load on the pancreas. There is increasing possibility of developing diabetes.

5) Salt

Salt increases the blood pressure, depletes adrenal glands, and causes emotional instability. Avoid table salt and foods high in salt especially those that are canned and preserved.

6) Fats:

Avoid the consumption of foods rich in saturated fats. Fats cause obesity and put unnecessary stress on the cardiovascular system. High fat is believed to increase the risk of breast, colon and prostate cancers.

Dietary guidelines for reducing stress:

- Eat a meal high in complex carbohydrates. It triggers release of the brain neurotransmitter serotonin, which soothes you. Good sources of carbohydrates include cereals and its products, whole pulses, vegetables, fruits, milk and milk products. Experts suggest that consumption of good carbohydrates(cereals, pulses, vegetables and fruits) helps in reducing stress as well as controlling blood glucose levels.
- Eat Foods high in fiber. Stress results in cramps and constipation. Eat more fiber to keep your digestive system moving. Your meal should provide at least 25 grams of fiber per day. Fruits, vegetables and grains are excellent sources of fiber.
- Eat plenty of vegetables. Eating more vegetables, can increase your brain's serotonin production. This increase is due to improved absorption of the amino acid L-Tryptophan. (Vegetables contain the natural, safe, form of L Tryptophan.) Meats contain natural L-Tryptophan also, but when you eat meat, the L-Tryptophan has to compete with so many other amino acids for absorption that the L-Tryptophan loses out. The net result is that you get better absorption of L-Tryptophan when you eat vegetables.

Thus one should consume foods like whole grains which promote the production of the brain neurotransmitter serotonin and increases your sense of well-being. We should also eat all types of vegetables as they are rich in minerals, vitamins, and phytochemicals, which boost immune response and protect against disease. One should reduce the intake of caffeinated beverages, foods that are rich in fat, as they are immune- depressing, (especially when it is because of stress) and reduce intake of animals foods as high protein foods elevate brain levels of dopamine and norepinephrine both of which are associated with higher levels of anxiety and stress.

In conclusion, stress may play a role in the onset of diabetes and also exacerbate the debilitating effects on a person with diabetes. It can have a deleterious effect on glycemic control and can affect one's lifestyle. Emerging evidence strongly suggests that interventions help individuals prevent or cope with stress which in turn has an important positive effect on quality of life and glycemic control.

Stress affects blood sugar control directly through the release of hormones and indirectly by disrupting self-management activities. Studies using more intensive one-to-one interventions have shown that stress management can improve glycemic control; this is the first demonstration that a simple, cost-effective group approach can have a meaningful therapeutic impact. In one of the studies it was found that intensive, home-based psychotherapy reduces diabetes-related stress among adolescents with chronically poorly controlled type 1 diabetes. Hence stress management is important for the psychological wellbeing of the diabetics who are at high risk for future health complications. A positive attitude in life always helps, so make it a part of your personality to cope better with diabetes and stress to lead a happy and healthy life.

■

Glycated Hemoglobin

Hemraj B Chandalia

Glycated hemoglobin (GHb) is the most important laboratory parameter for assessing the state of glycemic control in diabetes. It was described in 1970's and popularized in the next two decades [1]. The first report on the use of glycated hemoglobin from India was made in 1980 by Chandalia and Krishnaswamy from the Jaslok Hospital and Research Center [2]. The last decade witnessed extensive standardization programs for GHb in many countries round the world [3].

What is Glycated Hemoglobin?

It is that component of hemoglobin which has combined with glucose. It is expressed as percent of hemoglobin. It is formed by a post translational, non-enzymatic, substrate concentration-dependent process of combination of glucose with the terminal valine amino acid on the beta chain of globin. This is called HbA1c. As the blood glucose rises, it proportionally gets attached to hemoglobin in the erythrocytes. Hence, a single blood sample reflects faithfully the state of glycemia over the past 2-3 months of the lifespan of erythrocytes. Glucose also combines with other parts of the hemoglobin molecule. Additionally other sugars like fructose also combine with hemoglobin. These combination products, along with HbA1c produce a value higher than HbA1c by 1.5 – 2% and are called total glycated hemoglobins. Currently, only HbA1c is being reported by most laboratories, hence we shall confine our discussion to HbA1c.

Estimation of HbA1c

Sample for the estimation of HbA1c can be drawn at any time of the day, as the values are not affected by recent glycemia. HbA1c is stable in the sample for a period of one week or beyond, unlike blood glucose, which changes rapidly, even if the sample is collected in a fluoride tube. The method used to estimate HbA1c are many; High Performance Liquid Chromatography (HPLC), boronic affinity method and immuno turbidimetric method are employed currently. When used properly, these methods yield consistence results, so that intra-individual variation (same sample being estimated several times) shows a very low variation of < 2% [3].

Clinical Use of HbA1c

Monitoring control of Diabetes

HbA1c is a true reflection of mean blood glucose. This fact has been amply proven in the literature (Table 1). It mainly (90%) reflects previous two months of glycemia and to a less extent (10%) the previous third month of glycemia (Fig 1). When HbA1c estimation is done in the clinic setting, along with a blood glucose (Fasting, Postprandial or Random), the conclusion regarding glycemic control reached may not be same; in fact in about 50% of the patients blood glucose shows metabolic control one-step different (good vs fair or fair vs poor) and in about 7% of the patients it shows entirely different results (e.g. good vs poor) [4]. This results from the fact that the blood sugar can be manipulated by the patient by altering diet, exercise or medications on the day of the test, while HbA1c value is non- manipulable.

HbA1c has been used in all long term research studies. In the DCCT study, HbA1c was about 1% and in the UKPDS study about 2% lower in the intensively controlled patients, as compared to the group on standard therapy. This resulted in significant prevention of complications especially microvscular complications.

In type 1 diabetes, blood glucose values often fluctuate widely. It is difficult to draw any conclusion regarding the average blood glucose value without extensive calculations. HbA1c provides a correct assessment of average glycemia by a single blood test.

Limitations in clinical use

The fluctuations in blood glucose are not faithfully reflected in the HbA1c value. These can only be assessed by Self-Monitoring of Blood Glucose (SMBG) or Continuous Glucose Monitoring system (CGMS).

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It is not possible to adjust any treatment on the basis of HbA1c results. Very high or low HbA1c values can help decide about the basic necessities of tightening or relaxing control of diabetes but does not provide any clue regarding which treatment modality must be modified and to what extent.

HbA1c may be inaccurate in anemic states, mainly in the dynamic phase of anemia, when either there is active blood loss, hemolysis or rapid response to treatment [4]. In our country, iron deficiency anemia is very common. In the stable state of anemia, the HbA1c results are not altered, but in the dynamic phase the results often show low HbA1c because of an younger population of erythrocytes in circulation.

Genetically, HbA1c values can be different, depending upon the rate of glycation. However, this does not happen frequently. However, erythrocyte lifespan can vary in different populations, thus altering reference values. There is also a varying frequency of hemoglobinopathies in different populations. Hence, a population-specific reference value must be available for proper interpretation of HbA1c values in diabetics.

HbA1c in various complications

Renal failure: In this situation carbymalated compounds are increased, which can interfere with HbA1c assay in some systems. However, currently used three main systems described above are free of such interference. In renal failure, anemia occurs due to erythropoietin deficiency, often concomitantly with iron deficiency. This would alter HbA1c values except in the stable phase of anemia.

Pregnancy: The erythrokinetics are altered in pregnancy, in addition to iron deficiency. The ambient blood glucose is also low in pregnancy in non-diabetics. Thus HbA1c goals are stricter in pregnancy; about 1.5-2% below the usual goals (Table 2). In pregnancy, HbA1c is estimated at monthly intervals, because previous one month reflects 50% of the glycemic events (Fig 1). It is important for a type 1 or type2 diabetic to undertake pregnancy only when HbA1c is < 7 %; in fact it is feasible to achieve a value of < 6% in type 2, well motivated diabetic.

HbA1c goals

Of all goals set for diabetics, glycemic goals are important. (Table 2). Based upon the current evidence, overall the glycemic goals are stricter in recently diagnosed type 2 diabetics and pregnancy. They are a bit relaxed in type 2 diabetes of long standing duration and type 1 diabetes. They are further relaxed in diabetics with significant cardiovascular, renal, retinal and neurological complications.

HbA1c in diagnosis of Diabetes

As a laboratory parameter, HbA1c is now considered a more stable analate than even blood glucose. HbA1c can be estimated from a drop of blood from the finger- prick and also from a drop put on the filter paper and transported at ambient temperature. There are less pre-analytic errors in the estimation of HbA1c. Analytical errors have been now minimized in many countries where active HbA1c standardization has taken place. Hence, it is logical to use HbA1c in the diagnosis of diabetes. Chandalia and coworkers described this in 1982, where sensitivity of HbA1c in the diagnosis of diabetes was found to be 60 % and specificity close to 100% [5]. This issue has been studied again vigorously and similar data on the sensitivity and specificity have been reported (Table 3). Overall it means that while oral GTT detects more patient of diabetes, HbA1c, will miss the diagnosis in almost 40%. However, once HbA1c is clearly elevated (>6.5%), the diagnosis of diabetes is certain. Presently, a value of < 6.1% is considered normal, 6.1- 6.5% indicative of impaired glucose tolerance and > 6.5% as diagnostic of diabetes[6].

Standardization of HbA1c

First attempts towards standardization of HbA1c were made by National Glycated Hemoglobin Program (NGSP) in USA. The same criteria were used in DCCT study, hence DCCT/NGSP criteria are identical. Subsequently, International Federation of Clinical chemistry (IFCC) isolated a purified preparation of HbA1c and established that the reference range of this purified from is 1.5-2 % lower than that of NGSP values. IFCC also suggested that the values be reported as per their method, as mmol of HbA1c per mol of hemoglobin. This has caused considerable confusion in the literature, but for all clinical purposes the NGSP values are being used and will continue. It is possible to interconvert HbA1c values by different methods and also calculate mean blood glucose from HbA1c values (Table 4).

Table 1: Relationship of HbA1c with Mean Plasma Glucose

A_{1c} (%)	Mean Plasma Glucose	
	mg/dl	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

Source: ADA.V. Diabetes care. Diabetes care 2011; 34 (supp 1): S18.

Table 2: HbA1c Targets

Type 2 DM	Initial 2-5 years of disease	<6.5%
	5-10 years of disease	<7%
	>10 years of disease with cardiovascular, renal, retinal, neurological complications	<7.5%
Type 1 DM	With standard insulin therapy	<7.5%
	With intensified insulin therapy or insulin pump therapy	<7%
Pregnancy	Gestational DM	<6%
	Pregestational, type 2 DM	<6.5%
	Type 1 DM	<7%

Table 3: Sensitivity and specificity of HbA1c for detecting undiagnosed diabetes (fasting plasma glucose 7.0 mmol/l) at increasing HbA1c cut off levels

HbA1c cutoff (%)	Sensitivity	Specificity
5.6 (1 SD above normal mean)	83.4	84.4
6.1 (2 SD above normal mean)	63.2	97.4
6.5 (3 SD above normal mean)	42.8	99.6
7.0 (4 SD above normal mean)	28.3	99.9

Source: Rohlfing, et al, Diabetes Care, 2000

Table 4: Interconversion of Mean Blood Glucose and HbA1c

1)	Mean Blood Glucose (mmol/L) = 1.84 x IFCC.HbA1c Mean Blood Glucose (mmol/L)= 1.98 x DCCT(NGSP). HbA1c - 4.29
2)	NGSP.HbA1c = 0.915 (IFCC.HbA1c)+ 2.15%

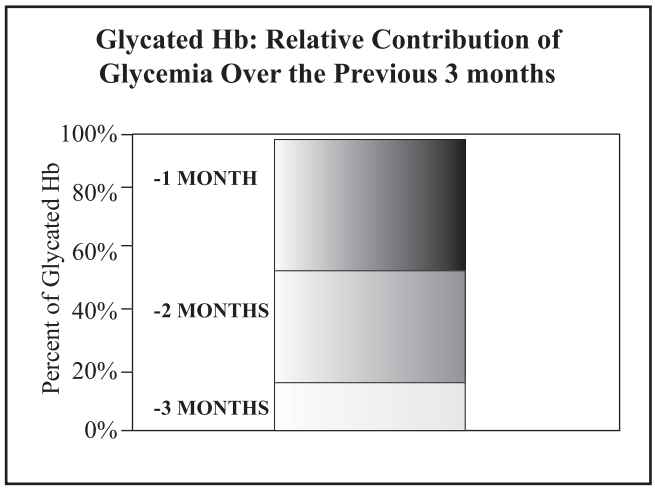

Fig 1: Glycated Hemoglobin: Relative Contribution of Glycemia Over the Previous 3 months

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ORGANISATIONAL NEWS

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Eligibility Criteria

Ordinary Membership

a) Graduates in Nutrition or Nursing (B. Sc and above), Pharmacist (B-pharm or above) with minimum 3 months of practical experience in Counseling people with diabetes; or 2 years of practical experience in any health care setting. Those applying within 5 years since basic graduation can be admitted as Members at a concessional rate, but they must fulfill other criteria.

b) Medical graduates recognized by Medical Council of India. Only those who have demonstrated abiding interest in diabetes education shall be admitted after due scrutiny by the Executive Council.

Documents to be submitted:

a) Application form duly filled and signed

b) Self attested photocopy of basic degree (Bachelors degree) certificate

c) Self attested photocopy of practical Experience certificate

d) Self attested photocopy of additional degree certificate

Submit your application with attachments (hard copy or soft copy) and cheque or demand draft by courier or through net banking or personally to Ms Sonal Modi at the following address:

103-104 Lady RatanTata Medical Center, M. Karve Road, Mumbai – 400 021

Tel: 91-22-2284 0244 Email id- **ademembers@gmail.com**

Life Membership fee:

Membership fee (Ordinary) – Rs.1000/-

Membership fee (within 5 years of basic graduation) - Rs. 500/-

MEMBERSHIP FORM

Association of Diabetes Educators (ADE)

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Address ……..……

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

E-mail id: ……..…….....

Educational Qualifications:……..……

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Work Experience: ……...……

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Currently employed at: ….……

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The money is payable in cash/ cheque/demand draft/ net banking.

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Name:	Association of Diabetes Educators	
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1. You will be together with all colleagues on one platform. You will be able to lobby altogether and establish your profession.
2. Quarterly Journal of Diabetes Education will be sent to you free.
3. Can attend the annual meeting at low registration charges.
4. You will be able to present your research and clinical work in the journal and annual meeting
5. In the long run, formation of Council of Diabetes Education may take place, thus giving professional status to the diabetes educators
6. Free access to Association of Diabetes Educators website which will carry agenda of Annual meeting, newsletter and placement services.

Watch

www.diabeteseducatorsindia.com

The website of Association of Diabetes Educators is expected to be operational by January, 2013

ANNUAL SCIENTIFIC CONFERENCE

OCTOBER 7, 2012

Time				
8.30 hrs - 10.00 hrs	**BREAKFAST & REGISTRATION**			
10 hrs - 10.30 hrs	**Inauguration by Chief guest:** Col. Dr R.R. Pulgaonkar, Chief Executive Officer,Jaslok Hospital and Research Centre, Mumbai **Release of the first issue of the Journal of Diabetes Education:** Dr R.D. Lele, Hon Chief Physician & Director, Nuclear Medicine Department, Jaslok Hospital and Research Centre; Emeritus Professor of Medicine & Ex-Dean, Grant Medical College, Mumbai			
Time	**Sessions**	**Chairpersons**	**Topic**	**Speaker**
10.30 hrs - 11.00 hrs	SESSION 1	**Shobha Udipi, Sunil Gupta**	Better adherence to diabetic care: How to motivate?	**Banshi Saboo**
11.00 hrs - 11.30 hrs			Quantitative sensory testing in diabetic neuropathy	**Benny Negalur**
11.30 hrs - 12.00 hrs	SESSION 2	**Saroja Raghavan, Vijay Vishwanathan**	Educating diabetic to prevent foot problems	**Vijay Vishwanathan**
12.00 hrs - 12.30 hrs			Glycated Haemoglobin	**Hemraj Chandalia**
12.30 hrs - 13.00 hrs			Artificial Sweeteners	**Sonal Modi**
13 hrs - 13.45 hrs	**LUNCH**			
13.45 hrs - 14.15 hrs	SESSION 3	**Salome Benjamin, Banshi Saboo**	Role of Diabetic educators in diabetes mellitus associated with pregnancy	**Sunil Gupta**
14.15 hrs - 14.45 hrs			Lifestyle interventions in diabetes	**Nisha Manikandan**
14.45 hrs - 15.15 hrs			Insights into insulin injection technique	**Paulami Choudhury**
15.15 hrs - 16.15 hrs	SESSION 4	**Coordinator- Pallavi Yajnik & Dhanashree Naik**	Interactive session on: Problem solving diabetes education case studies	**Vandita Gupta, Pallavi Yajnik, Dhanashree Naik, Sandhya Shankar, Preeti Thakur**
16.15 hrs - 16.30 hrs	**TEA**			
16.30 hrs - 17.30 hrs	SESSION 5	**Coordinator - Hemraj Chandalia**	Open Forum: Questions and Answers - All Participants and Faculty	

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7. As of April, 2010.

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- Powerful HbA1c reduction of 1.8 %[1]
- Proven Sustainability of HbA1c reduction up to 2 years[2]
- Lesser Glycemic fluctuations vs Sitagliptin[3]
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• Based on AACE, ADA and NICE guidelines year 2012 which recommends DPP4 in monotherapy failures 1. Adapted from Gerich J. DPP-4 inhibitors: What may be the clinical differentiators? diabetes research and clinical practice 90 (2010) 131-140 2. Adapted from Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study D. R. Matthews, S. Dejager, B. Ahren, V. Fonseca, E. Ferrannini, A. Couturier, J. E. Foley & B. Zinman, Diabetes, Obesity and Metabolism 12: 780-789, 2010 3. Adapted from Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations: Raffaele Marfella, Michelangela Barbieri, Rodolfo Grella, Maria Rosaria Rizzo, Giovanni Francesco Nicoletti, Giuseppe Paolisso: Journal of Diabetes and its Complications 24 (2010) 79-83 4. Adapted from Schweitzer, S. Damager, J. E. Foley, A. Couturier, M. Liguoros-Saylan & W. Kothny - cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes populatio: Diabetes, Obesity and Metabolism 12: 485-494, 2010 5. Adapted from Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥75 years: a pooled analysis from a database of clinical trials A. Schweizer, S. Dejager, J. E. Foley, Q. Shao & W. Kothny: Diabetes, Obesity and Metabolism 13: 55-64, 2011 6. Adapted from Poster Presentation # 840. Presented at: 47th Scientific Sessions of the European Association for the study of Diabetes; September 12-16, 2011; Lisbon, Portugal

For the use of Registered Medical Practitioner only. For full prescribing information contact Novartis.

Basic Succinct Statement - GalvusMet®

Presentation: Vildagliptin/Metformin hydrochloride fixed combination; 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg tablets. **Indications:** •GalvusMet® is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM) whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. **Dosage:** •Do not exceed the maximum recommended daily dose of vildagliptin (100 mg). •Should be given with meals. •Starting dose for patients inadequately controlled on vildagliptin monotherapy: 50 mg/500mg twice daily and gradually titrated after assessing adequacy of therapeutic response. •Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy: 50 mg/500mg, 50 mg/850 mg or 50 mg/1,000 mg once or twice daily. • Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets: 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg. **Contraindications:** Known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients •renal disease or renal dysfunction •congestive heart failure •acute or chronic metabolic acidosis including diabetic ketoacidosis with or without coma •should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. **Precautions/Warnings:** •Risk of lactic acidosis. •Monitoring of renal function. •Caution with concomitant use of medications that may affect renal function or metformin hydrochloride disposition. •Should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. •Discontinue treatment in case of hypoxaemia. •Temporary discontinuation in patients undergoing surgical procedure. •Excessive alcohol intake to be avoided. •Not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. Liver function tests (LFT) to be performed prior to treatment initiation, at three-month intervals during the first year and periodically thereafter. Withdrawal of therapy with GalvusMet recommended if an increase in AST or ALT of 3X upper limit normal or greater persist. Following withdrawal of treatment with GalvusMet and LFT normalisation, treatment with GalvusMet should not be reinitiated. •Risk of decreased vitamin B12 serum levels. •Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. •Risk of hypoglycaemia. •May be temporarily withheld in case of loss of glycaemic control. •Should only be used in elderly patients with normal renal function. •Not recommended in paediatric patients. **Pregnancy:** Should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. **Lactation:** Should not be used during breast-feeding. **Interactions:** •Interactions with Vildagliptin: low potential for drug interactions, no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. •Interactions with metformin hydrochloride: furosemide, nifedipine, cationic drugs, drugs tending to produce hyperglycaemia, alcohol. **Adverse reactions:** •Vildagliptin: Rare cases of angioedema. Rare cases of hepatic dysfunction (including hepatitis). •Vildagliptin monotherapy - Common: dizziness – Uncommon: headache, constipation, oedema peripheral. •Metformin monotherapy – Very common: nausea, vomiting, diarrhoea, abdominal pain, loss of appetite. Common: metallic taste. Very rare: decrease of vitamin B12 absorption, lactic acidosis, liver function test abnormalities, hepatitis, skin reactions such as erythema, pruritus and urticaria. •Other effects with combination of Vildagliptin and Metformin - Common: headache, tremor, dizziness. •Post-marketing experience: Rare: hepatitis (reversible with drug discontinuation)- Uncommon: pancreatitis, urticaria. **Packs:** Box containing 6 strips of 10 tablets each. **Note:** Before prescribing, consult full prescribing information available from Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai- 400 018, Tel: 022 2495 8888.

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