2013 Asia-Pacific Diabetes Symposium
Diabetes Mellitus: pyramids, paradigms and possibilities
Kuala Lumpur, Malaysia - 11-12 May 2013
General information

Venue
The symposium will take place at the:
Le Méridien Kuala Lumpur
2 Jalan Stesen Sentral,
Kuala Lumpur Sentral
Kuala Lumpur - Malaysia

Language
The official language of the symposium is English.

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2013 Asia-Pacific Diabetes Symposium
Diabetes Mellitus: pyramids, paradigms and possibilities

Aim of the symposium
The burden of type 2 Diabetes Mellitus (T2DM) continues to grow in the Asia-Pacific region, in parallel with the acquisition of a western diet and lifestyle and the increasing occurrence of obesity. As a consequence, the morbidity and mortality associated with T2DM micro- and macro-vascular complications and other comorbidities are also increasing, with a growing effort from the local healthcare systems and its professionals. To face such challenges, updated knowledge and skills are essential to better manage T2DM according to the new international treatment guidelines and to the recent evidence-based medicine findings for its complications’ care.

Serono Symposia International Foundation is honoured to organize the 2013 Asia-Pacific Diabetes Symposium “Diabetes Mellitus: pyramids, paradigms and possibilities” in collaboration with the Malaysian Endocrine and Metabolic Society.

The aims of this symposium are to review the most recent achievements in T2DM management and care of its complications and comorbidities, including cardiovascular diseases, renal function impairment and peripheral neuropathy, and to provide participants with solutions for optimizing patient management in daily clinical practice.

Learning objectives
After attending the educational live symposium, the learners will be able to improve their clinical practice on the following aspects of T2DM:
• Prevention and early treatment of situations with altered glucose metabolism
• Patient-centered guidelines for treating hyperglycemia in T2DM patients
• Relationship between T2DM and its complications and comorbidities, including cardiovascular disease, nephropathy and cancer
• Role of B vitamins in managing diabetic peripheral neuropathy and other conditions

Target audience
Diabetologists, Endocrinologists, Internal Medicine specialists, and all the healthcare professionals dealing with T2DM and its complications and comorbidities, including general practitioners (GPs).

Accreditation
Serono Symposia International Foundation (www.seronosymposia.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The conference 2013 Asia-Pacific Diabetes Symposium “Diabetes Mellitus: pyramids, paradigms and possibilities” (11-12 May 2013 – Kuala Lumpur, Malaysia) is designated for a maximum of 9 (nine) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.
We value your opinion!

We are continually trying to develop and improve our educational initiative to provide you with cutting-edge learning activities. During this symposium you will be asked to answer a real time survey and after this educational event you will be receiving an online survey to help us to better tailor our future educational initiatives.

We thank you for participating!

Serono Symposia International Foundation adheres to the principles of the Good CME Practice group.
Scientific organizers

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Kuala Lumpur, Malaysia
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Malaysian Endocrine and Metabolic Society (MEMS)

Mohamed Mafauzy
Health Campus University Sains Malaysia
Kelantan, Malaysia
and
Malaysian Endocrine and Metabolic Society (MEMS)

Serono Symposia International Foundation designed this programme in partnership with the Malaysian Endocrine and Metabolic Society.

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Brahman Mitra Mandal Society
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Gunupati Vijaya Kumar
Apollo Speciality Hospital
Diabetes Medicare Centre
Chennai, India
## Scientific programme

### Saturday - 11 May 2013

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**Chaicharn Deerocchanawong**
Declared no potential conflict of interest.

**Roberto C. Mirasol**
Declared no potential conflict of interest.

**Mohamed Mafauzy**
Declared no potential conflict of interest.

**Bipin Sethi**
Declared no potential conflict of interest.

**Abdulrazzaq Ali Al Madani**
Declared no potential conflict of interest.

**Hui Yao Lan**
Declared no potential conflict of interest.

**Chionh Siok Bee**
Declared receipt of honoraria from the ISCD/IOF and from Build program in 2012 for osteoporosis lecture.

**Made Ratna Saraswati**
Declared no potential conflict of interest.

**Elizabeth Paz-Pacheco**
Declared receipt speakers’ honoraria from Astra-Zeneca, Sanofi-Aventis, MSD, Lilly, Boheringer Ingelheim. Declared to be member of a company advisory board, board of directors or other similar group of: Astra-Zeneca, Novo Nordisk, Sanofi-Aventis, MSD, Lilly. Declared participation in a company sponsored speaker’s bureau of: Astra-Zeneca, Sanofi-Aventis, MSD, Lilly, Boehringer Ingelheim.

**Debmalya Sanyal**
Declared no potential conflict of interest.

**Gunupati Vijaya Kumar**
Declared no potential conflict of interest.

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**Nor Azmi Kamaruddin**

**S.M. Bandukwala**
L1 - Epidemiology of diabetes: reasons of an epidemic in developing countries

Juliana Chan
Department of Medicine and Therapeutics, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, Hong Kong, China

There is an epidemic of diabetes in Asia. Type 2 diabetes develops in Asian patients at a lower mean body mass index (BMI) compared with those of European descent. At any given BMI, Asians have a greater amount of body fat and a tendency to visceral adiposity. In Asian patients, diabetes develops at a younger age and is characterized by early β cell dysfunction in the setting of insulin resistance. Large scale studies in Asians have reported novel genomic variations in loci encoding growth regulation, beta cell development and cellular signaling. While the high rates of gestational diabetes in Asian women may reflect this genetic predisposition, the in utero environment of hyperglycemia may amplify the risk of diabetes and obesity in their offspring, setting up a vicious cycle of “diabetes begetting diabetes”.

Adding to this complexity are cultural factors such as consumption of foods with high glycemic indexes, environmental pollutants, chronic low grade infections and psychosocial stress which worsen insulin resistance and accelerate beta cell failure. This combination of gluco-lipotoxicity and inflammation culminate into the increasingly early onset of diabetes and its comorbidities including cardiovascular-renal disease and cancer.

Despite these daunting trends, there are also pilot programs in Asia which have demonstrated the power of using protocols and teams to raise awareness, stratify risk, treat to multiple targets and reinforce compliance to reduce the risk of diabetes and its complications. To achieve these complex goals, a top down and bottom up approach will be required to mobilize the community and relevant stakeholders to take concerted actions to prevent the preventables.

References:
2 - Ma RC, Chan JC Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann NY Acad Sci. 2013 Apr;1281(1):64-91
The rapid increase in the prevalence of type-2 diabetes, obesity and associated complications (diabesity) is a major global health problem. Recent clinical trials have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of type 2 diabetes. For overweight and obese patients, a modest weight-loss goal of 5–10% can substantially reduce the risk of diabetes. Moderate-intensity physical activity such as brisk walking for at least 150 minutes per week also plays an important role in reducing diabetes risk, even in the absence of weight loss. The protocols employed in most lifestyle intervention trials are labor intensive and require dedicated staff and resources, raising issues about the economics of implementing these programs. Analyses of the costs of various strategies are conflicting, and two fundamental questions have emerged. First, if we elect to treat pre-diabetes, which of the strategies is the most cost-effective? Second, is it more economically prudent to start such a program in patients who are at high risk for diabetes, or should treatment be initiated only after diabetes has developed?

Lifestyle intervention has been conclusively proven effective in reducing diabetes risk, but for such an approach to be broadly implemented, it must be translated into community-based settings that are both accessible and affordable. Although such translation efforts are in their infancy, a number of significant efforts have been initiated. Such results reinforce the feasibility of effective community-based lifestyle intervention strategies for diabetes prevention in diverse populations and in varied settings. However, much remains to be done to gain commitment from insurers and health care systems to ensure broad implementation for high-risk populations.

For patients who are unable to achieve these lifestyle goals or those who progress despite exercising and losing weight, metformin has also been proven effective, especially in younger obese patients. Acarbose, when tolerated at the maximum effective dose, may also confer a moderate risk reduction. Data regarding thiazolidinediones are promising but the reports of cardiovascular and fracture risk make this option less attractive as a prevention strategy. However, none of these medications are as robust in diabetes prevention as the lifestyle intervention strategies, and cost-effectiveness analyses suggest that pharmacotherapy may have greater financial costs. Perhaps the most pressing clinical question remaining is whether these prevention strategies will reduce the vascular complications of diabetes that are the cause of the greatest financial burden and personal suffering in patients with diabetes. Prevention of diabesity is our most powerful intervention, and successful implementation of these proven strategies should be the focus of our efforts.
Diabetes mellitus remains one of the top leading causes of morbidity and mortality in the world. It also has been shown from recent data an increasing and earlier onset of diabetes complications seen in the Asia Pacific region. Data from the UKPDS, ACCORD, ADVANCE and VADT have shown increasingly complex regimens in terms of treating Type 2 diabetes and its complications. Several agents are now available to treat diabetes and hopefully delay the onset of complications with good blood glucose control. As a result, many clinicians are in a quandary of what drug to use in a particular patient. The ADA and EASD convened in a task force to come up with common evidence-based guidelines for the management of hyperglycemia in Type 2 diabetes mellitus. The guideline was conceptualized within the context of the needs, preferences and tolerances of each patient. It further stresses that individualization is the cornerstone to success. It is the intent of the authors (Inzucchi, et al.) to encourage appreciation of the variable and progressive nature of Type 2 DM, the specific role of each drug, the patient and disease factors that drive clinical decision making and the constraints imposed by age and co morbidity.

Hence considerations for more stringent (HgbA1c 6-6.5%) control of blood sugar in patients with short disease duration, long life expectancy, no significant CVD, less hypoglycemia risk. Conversely, less stringent control (HgbA1c 7.5-8%) are appropriate for patients with history of severe hypoglycemia, limited life expectancy, advanced complications with extensive co morbidity conditions.

The ultimate aims of controlling glycemia are to avoid acute symptoms of hyperglycemia (hyperosmolar non ketotic syndrome and ketoacidosis), and to prevent in the long term the development of diabetes complications without affecting adversely the patient quality of life.

Metformin remains the most widely used first line drug in diabetes treatment. It is considered weight neutral with chronic use and has low risk to develop hypoglycemia. It is associated with GI side effects and should not be used in patients with advanced renal disease. Sulfonlureas, thiazolidinediones, GLP-1 receptor agonists, DPP-4 and insulin will be the next line drugs in combination with metformin. Ultimately, most patients will require insulin therapy alone or in combination with other agents to maintain glucose control. All treatment decisions should be made in conjunction with the patient, taking into consideration his/her preference, needs and values. Comprehensive cardiovascular reduction should be the major focus of therapy.

References:
Metformin has been in clinical use for more than 55 years and is the first line of treatment for type 2 diabetes mellitus. It works mainly by decreasing hepatic glucose production and improving peripheral glucose uptake. The United Kingdom Prospective Diabetes Study (UKPDS) is the first study to show that metformin significantly reduced any diabetes related endpoint and in the post-trial monitoring, there was also a significant reduction in myocardial infarction and mortality. Several observational studies had also shown that metformin treatment significantly reduced mortality and adverse cardiovascular outcomes compared to sulphonylureas. There are several studies which showed that metformin also reduced the risk of cancer and cancer mortality. However, metformin can cause GI side effects and is the main cause of metformin discontinuation. The introduction of extended release (XR) formulation has improved GI tolerability and enables many patients to remain on metformin. The other worry with metformin is its’ risk of lactic acidosis. However, systemic reviews and meta-analysis have not shown that metformin therapy is associated with an increase risk of lactic acidosis compared with other antihyperglycemic treatments. In patients with renal impairment, there is a recent guideline that metformin can be used in patients with an eGFR as low as 30 mL/min per 1.73m². There are also studies to show that metformin did not increase risk of adverse events in patients with cardiac failure and liver dysfunction. On the contrary, metformin has been shown to improve survival in patients with heart failure and decrease risk of hepatocellular carcinoma in patients with liver cirrhosis. In real life clinical practice, studies had shown that many patients were still prescribed metformin despite active contraindications.
Abstract not in hand at the time of printing.
Diabetes is associated with increase in the cardiovascular morbidity and mortality. There are factors inherent to the disease that amplify the risk and some of the treatment modalities do the same as well.

Hypertension, dyslipidemia and endothelial dysfunction are the factors that predispose to atherosclerosis and diabetes tends to worsen each one of them. There has been some indication that the postprandial hyperglycemia is more relevant to the aggravation of the CV risk though this has not been borne out in any prospective trial, the relative contribution of hyperglycemia to CV events remains a subject of debate but is certainly greater in Type 1 than in the Type 2 subjects.

Management of diabetes alone confers protection when the control is intensified at diagnosis or as close to the onset as is possible, efforts later on in the disease are unlikely to show similar results and in some subjects may even be harmful. Certain drugs used in pharmacotherapy of diabetes may worsen the risk by causing hypoglycemia or worsening dyslipidemia and this has led to revised guidelines for antihyperglycemic drug approval process.

Multifactor interventions in subjects with microalbuminuria in Steno Hospital clearly demonstrated that this approach is able to markedly decrease the mortality as also the CV events.

What the new antihyperglycemic drugs hold for CV risk amelioration will be borne out by the long term CV outcome trials.
Abstract not in hand at the time of printing.
Diabetic nephropathy is a major cause of end stage kidney disease (ESKD) in most parts of the world. At diagnosis up to 35% of patients exhibited some form of nephropathy either albuminuria or impaired kidney function. Hyperglycaemia induced metabolic and haemodynamic changes mediate the injury responsible for the development of kidney disease. It is characterised by excessive proliferation of extracellular matrix with thickening of glomerular and tubular basement membranes and increased amount of mesangial matrix, which ultimately progress to glomerulosclerosis and tubulo-interstitial fibrosis.

On average the decline in GFR varies depending on the stages of the renal impairment as well as the underlying aetiology of diabetes either type 1 or 2. In those with no proteinuria the rate of decline of GFR among type 1 DM is 1.2-3.6 ml/min/year while for type 2 is 0.96 ml/min/year. With the development of proteinuria the rate of decline of GFR increased to 9.6-12 ml/min/year in type 1 and 5.4-7.2 ml/min/year in type 2. The presence of proteinuria is a very important prognostic marker not only in terms of the rate of progression of renal impairment but also in terms of CVD risk. Those with overt proteinuria increased the risk of developing ESKD by up to two to three folds. Without any specific intervention more than 50% of type 1 DM with overt proteinuria developed ESKD over a ten year period while only 20% of those with type 2 and overt proteinuria do so.

In a multivariate regression analysis, higher baseline proteinuria, systolic blood pressure (SBP), HbA1c, GFR, age and degree of diabetic retinopathy were significantly associated with increased rate of decline in GFR. While during follow-up, elevated mean albuminuria, SBP, HbA1c, lower hemoglobin, heavy smoking and the presence of diabetic retinopathy were significantly associated with increased decline in GFR. Similarly in regression analysis studies, higher baseline albuminuria, HbA1c, and SBP, together with lower GFR and hemoglobin, were significantly associated with shorter time to doubling of serum creatinine or ESKD. Higher baseline albuminuria, HbA1c, SBP and age were significantly associated with increased mortality.

In terms of slowing the progression of diabetic renal impairment the 5 principles of management can be primarily summed up by the mnemonic BD-CAP ie Blood Pressure, Diabetes, Cholesterol, ACEI or ARB and Protein restriction. The ACCORD trial which specifically looked at lower BP targets in diabetics failed to demonstrate any benefits other than slowing the progression of proteinuria. Indeed among the intensive arm there were those who suffered a deterioration in eGFR. In patients with hypertension RAS inhibition has been shown to delay the onset of microalbuminuria while ARBs have not been shown to prevent the onset of proteinuria in normotensive patients. Studies in patients with various stages of renal impairment have shown that protein restriction slows the progression of proteinuria, GFR decline and the development of ESKD. However recent studies have revealed conflicting results. Despite that protein restriction should be introduced especially in patients on ACEI or ARB whose GFR seems to be deteriorating despite good glycaemic and blood pressure control.
Diabetes mellitus is the leading cause of end stage renal disease (ESRD) and is responsible for more than 40% of ESRD worldwide. Current therapies directed at retarding the progression of diabetic nephropathy (DN) include intensive glycemic and optimal blood pressure control, reduction in proteinuria/albimunuria, interruption of the renin-angiotensin-aldosterone system through the use ofangiotensin converting enzyme inhibitors (ACEI) and angiotensin type-1 receptor blockers (ARB), along with lipid lowering agents. However, the renal protection provided by these therapeutic approaches remains incomplete. More effective approaches are urgently needed. Recently, several novel therapeutic strategies have been explored in treating DN patients including PPAR-gamma agonists, endothelin blockers, protein kinase C (PKC) inhibitors, advanced glycation end-products (AGEs) inhibitors, angiotensin converting enzyme-2 (ACE-2), selective vitamin D activation, inflammation modulation, TGF-β/connective tissue growth factor (CTGF) inhibitors. The benefits and risks of these agents are still under investigation. This presentation aims to summarize the utility of these therapeutic approaches for DN and provide the molecular-link for these treatment strategies. In addition, novel approaches for future nephro-protection are highlighted.
Diabetes and cancer are both common diseases that have serious impact on health worldwide. Epidemiologic evidence shows that diabetes appears to convey an increased risk for certain cancers, such as liver, pancreatic, and endometrial cancers (twofold or higher increase), as well as colorectal, anal, stomach, bladder and kidney cancers (approximately 1.2-1.5 fold increase)\(^1,2\). However, a reduced risk for prostate cancer has been seen in several studies of men with diabetes. Both diseases have many common risk factors, such as older age, male sex, ethnicity such as Afro-American race, smoking, alcohol consumption, poor diet, physical inactivity, and overweight or obesity in association with the metabolic syndrome. Obesity is common in diabetes patients, but diabetes appears to confer additional risk to obesity for cancer overall, excluding prostate cancer\(^2\).

The possible biologic links between diabetes and cancer include hyperinsulinaemia, particularly in the portal venous circulation, increased IGF-1 levels, increased bioavailable oestrogen [in men and women] and testosterone levels [in women but not men]; hyperglycaemia; and increased inflammatory cytokines such as PAI-1, IL-6, tumour necrosis factor, monocyte chemoattractant factor, adiponectin and leptin.

Different diabetes therapies appear to exert an influence on cancer risk as well. Metformin has been shown in human observational studies to be associated with a lower risk of cancer compared to other therapies\(^3\). Recent meta-analyses of observational studies have shown that Metformin treatment was associated with a significantly reduced risk of liver\(^4\) and colorectal\(^5\) cancers, by approximately 40-60%. Insulin or sulphonylurea treatment conferred an approximately 1.3 fold increased risk\(^6\). With GLP-1 analogues and DPP-4 inhibitors, animal studies have found increased \(\beta\)-cell proliferation, and a recent study based on the FDA database of reported adverse events show that pancreatic cancer was more commonly reported with the use of these therapies\(^6\). In patients who develop cancer, having diabetes is associated with an approximately 1.1-1.4-fold higher cancer mortality rate, particularly for liver, pancreas, colorectal, and possibly breast, ovary, endometrial, bladder and lung cancers, in addition to a 1.6-fold increase in all-cause mortality\(^7,8\).

However, cancer mortality rates are also influenced by diabetes therapy. Metformin monotherapy is associated with a reduced cancer mortality by 15-60%, while insulin and sulphonylurea monotherapy are associated with increased cancer mortality, by 1.2-2.0 fold and 1.1-1.3 fold respectively\(^9,10\).

References:
5. Zhang ZJ et al. Reduced risk of colorectal cancer with Metformin therapy in patients with type 2 diabetes. Diabetes Care 2011;34:2323-2328
Diabetes is a chronic disorder with consequence of chronic complication in its natural history. It has been well indicated that oxidative stress is involved in the pathogenesis of diabetes, as well as in the pathogenesis of its chronic complications.

Micronutrients are substances which are needed in tiny amounts, however they are essential for proper body functions, for example enable the body to produce enzyme and hormones. Some of the micronutrients such as potassium, magnesium, and possibly zinc and chromium, are essential in carbohydrate metabolism, and deficiencies of these minerals may predispose to carbohydrate intolerance. Micronutrients deficiency in diabetes patient may also cause other co morbidities. Several micronutrients have also potent antioxidant properties. These include carotenoids, vitamins E, vitamin C, selenium, and some of the vitamins B including folate, pyridoxine, and cyanocobalam. In the other side, some micronutrients have prooxidants properties such as ferritin and homocysteine, which are elevated in diabetes.

Some studies have shown that there is different micronutrient status in diabetes patient compare with people without diabetes. It is not clear whether the difference status is part of the cause of the disease or a consequence of diabetes, including hyperglycemic state and its complication.

Most of these micronutrients are available from daily food intake. Information of micronutrient contain in each food is important however this information is not always available. Nutrition therapy is an important part of diabetes management. Patients may avoid certain foods in order to cut their calorie intake. Some oral anti diabetic medication may reduce the micronutrient uptake from the gastrointestinal. Other than lack of intake, patient with diabetes may lose more than non diabetes. In hyperglycemic state, patients lose more urine, together with other electrolyte.

The requirement of micronutrients is not easy to determine. Measurement of each micronutrient in the blood will be costly, and it is not accurately reflect the functionally quantities in the body. Since micronutrient deficiencies known impair the synthesis in mitochondria which result in DNA damage, and cell senescence, a multivitamin and mineral supplementation is seems to be one low-cost way to ensure intake of the Recommended Dietary Allowance of micronutrients throughout life. In diabetes, routine supplementation with antioxidants, such as vitamins E, C and carotene sound rational to reduce oxidative damage associated with high serum glucose concentration however it is not advised because of lack of evidence of efficacy and concern related to long-term safety. In daily practice, the challenge then is to determine what micronutrient is recommended to take, to which patient, in what dose, when to start, and for how long.
Diabetic polyneuropathy is predominantly a symmetrical sensory affection, primarily affecting the distal portions of the lower extremities. Approximately 10-20% of patients present with the nerve damage at time of diagnosis of diabetes. This suggests that neuropathy involves a progressive nature, implying that early impairment of glucose handling as seen in prediabetic states leads to neuropathy. As the complication progresses, sensory loss ascends and appears in the hands, the typical "stocking-glove" sensory loss. Motor involvement with frank weakness occurs in the same pattern, appearing even later.

Multiple etiologies have been linked to the neuropathy syndromes. Both direct nerve cell damage from hyperglycemia, and neuronal ischemia from alterations in neurovascular flow in pathways that include the polyol, hexosamine and protein kinase C pathway and production of advanced glycation end-products and increased oxidative stress.

Diagnosis for routine clinical practice may be carried out through the Michigan Neuropathy Screening Instrument. The Michigan Diabetic Neuropathy Score, consisting of a quantitative neurologic examination and nerve conduction studies, is useful for diagnosing and staging diabetic neuropathy for clinical trials and epidemiologic studies. Additional useful screening assessments include the United Kingdom screening test and the tuning fork test.

Devastating complications such as amputation for infected, nonhealing ulcers is possible. As such, early detection of diabetic polyneuropathy through recognition of symptoms and physical findings in diabetes is critical.

References:
Diabetic neuropathy (DN) is a common complication of diabetes, development and progression of DN is largely due to hyperglycemia but numerous biochemical mechanisms like increased oxidative stress seem intimately associated. There is lack of response and unwanted side-effects of conventional pharmacological management of painful DPN. Therefore multifaceted combinatorial therapies including dietary supplements like vitamin Bs and other agents inhibiting pathogenic mechanisms are probably necessary. Thiamine (B1), pyridoxine (B6) and cyanocobalamin (Cbl) or vitamin B12 are the major vitamins of B complex. They act mainly as coenzymes of different reactions and may have neuroprotective effects.

In type 2 diabetic patients, long-term treatment with metformin is associated to lower plasma vitamin B12 and higher homocysteine levels. Metformin, dose dependently, impair calcium-dependent membrane activity in the ileum, including uptake of Cbl-intrinsic factor complex in a manner which may be partially reversed by increasing calcium intake. It may be reasonable to screen for Cbl deficiency every 1-2 years in diabetic patients receiving long-term metformin therapy. Some studies have shown that vitamin B12 in DN provides greater symptomatic than changes in electrophysiological results, but high-quality, double-blind randomized controlled trials (RCTs) are needed to confirm the effects of routine supplementation.

The fat-soluble form of vitamin B1, called benfotiamine, has been used to treat DN. Benfotiamine increases transketolase activity blocking three major molecular pathways leading to hyperglycemic damage. Six weeks treatment with 300-600 mg/day of benfotiamine improved “neuropathy symptom score”, greater with increasing dose and duration. But double-blind RCTs are required for further evaluation.

Low levels of vitamin B6 have been reported in patients with diabetic neuropathy but not without neuropathy. One small-scale, 6-week trial observed symptomatic improvement, three subsequent double-blind RCTs found no benefit. Further studies are needed for better clarity.

Alpha-lipoic acid (ALA), a naturally occurring dithiol antioxidant and may benefit DN. A systematic review of 15 trials concluded that short-term treatment with parenteral ALA, 600 mg/d, reduced neuropathic symptoms and deficits. In SYDNEY 2 trial, treatment with oral dose of 600 mg once daily ALA for 5 weeks provided the optimum risk-to-benefit ratio in improving neuropathic symptoms and deficits in patients with DN. ALA has a limited side effect profile and is approved in Germany for DN. As more research on the long-term benefits of alpha-lipoic acid become available, statements concerning the long-term safety and clinical effectiveness can be made.

There is also no conclusive evidence of effectiveness of gamma-linolenic acid (GLA) acetyl-carnitine and another antioxidant vitamin E. Vitamin D deficiency is an independent risk factor for diabetic peripheral neuropathy and RCTs are required to confirm the role of Vitamin D supplementation in DN.

In conclusion, role of vitamin B1, B6 & B12 in treatment of diabetic neuropathy is not established and not recommended as a standard or routine therapeutic option without underlying deficiencies and requires RCTs for clarity. Diabetics should acquire daily vitamin and mineral requirements from natural food sources. Assessment of B12 in peripheral neuropathy is prudent in patients on high dose metformin. Currently, ALA is approved in Germany for diabetic neuropathy.
There is proposed role of vitamin D in Coronary artery disease, Hypertension, Diabetes Type I and Type 2, Osteoarthritis, Depression, Epilepsy, Polycystic ovaries, musculoskeletal Pain, Autoimmune Disease, Multiple Sclerosis, Cancers, Falls in the Elderly and Pregnancy and Lactation. Small doses of Vit D [800IU] for 8 weeks decreased BP and pulse rate. BP is reduced significantly by ultraviolet radiation comparable to about oral intake of 3,000 IU of vitamin D a day. BP not routinely reduced by small amounts of vitamin D. Low Vit D levels assoc with insulin resistance and Beta-cell dysfunction, postprandial glucose and insulin sensitivity. There is direct effect of vitamin D on insulin secretion – Presence of specific vitamin D receptors in pancreatic beta –cells, impaired insulin secretory response in mice lacking functional vitamin D receptors. There is presence of the vitamin D response element in the human insulin gene promoter. Vitamin D 400-800 iu per day associated with improved mood within 5 days. Vitamin D levels inversely correlated to colon cancer mortality. Vitamin D plays important role in the pathophysiology of various diseases. Vitamin D and Ca^{2+} supplementation lead to improvement in –Weight, BMI, Insulin resistance, Prevention of development of T2DM, Longevity.

References:
Diabesity is a coined term given when Diabetes and Obesity are together in the same individual. This is a state of malnutrition and imbalance between energy input and expenditure. Diabesity also includes metabolic disturbances of insulin resistance, hyperinsulinemia and hyperglycemia. Also associated with co morbid conditions like hypertension and dyslipidemia leading to micro and macro vascular complications.

The most important aspect in management of diabesity is Life Style Modification (LSM). Apart from exercise, diet advise include restriction in calories and many food items. Due to the metabolic abnormalities there is decreased absorption and increased excretion of several essential nutrients. The so called balanced diet is deficient in essential nutrients which have an important role in alleviation of metabolic disturbances of diabesity.

Goals of nutritional supplem entation:
1. Supply daily requirement of nutrients
2. Improve metabolic disturbances
3. Improve immunity
4. Prevent micro and macro vascular complications.

There are evidences showing the essential role of vitamins, nutraceuticals, minerals and micro nutrients. In diabesity nutritional supplem entation is a convenient and inexpensive way to ensure adequate intake of crucial blend of vitamins and minerals.
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