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HEALTH TECHNOLOGY ASSESSMENT REPORT

MINISTRY OF HEALTH MALAYSIA

# NUTRITIONAL THERAPY AS A COMPLEMENT FOR DIABETES & HYPERTENSION

MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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# Health Technology Assessment Report

## NUTRITIONAL THERAPY AS A COMPLEMENT FOR DIABETES & HYPERTENSION

**DISCLAIMER**

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organisations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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# DISCLOSURE

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# EXECUTIVE SUMMARY

Globally, magnitude of non-communicable diseases has been rapidly growing and constitutes one of the major public health challenges. In 2008, 63% of global deaths were due to non-communicable diseases. In the United States (2008), 68 million populations were estimated to have hypertension, which increases the risk for the leading causes of death, heart disease and stroke. Similarly, Diabetes Mellitus (DM) epidemic is accelerating in the developing world, with an increasing proportion of affected people is in the younger age groups. In Malaysia, the prevalence of both hypertension and Type 2 DM (T2DM) is also rising as demonstrated in the National Health and Morbidity Survey 2011 whereby hypertension among adult of 18 years and above was 32.7% and T2DM of 15.2%. There was an increasing trend in prevalence with age from 8.1% for hypertension and 2.1% for diabetes in the 18-19 years old age group reaching a peak of 74.1% for hypertension and 36.6% for diabetes among 65-69 year olds. These chronic diseases have common risk factors and underlying pathologic mechanisms that may be modified by nutrients.

According to WHO criteria, prediabetes is considered with reading of Fasting blood sugar (glucose) at the level of: 110 to 125 mg/dL (6.1 mmol/l to 6.9 mmol/l), whilst American Diabetes Association (ADA) criteria suggests 100 to 125 mg/dL (5.6 mmol/l to 6.9 mmol/l ). For prediabetics, two hour glucose tolerance test reading showed the blood sugar level of 140 to 199 mg/dL (7.8 mmol/l to 11.0 mmol/l) and HbA1c is in the range of 5.7 to 6.4 percent.

According to similar WHO criteria, diabetes is considered with reading of a random venous plasma glucose concentration > 11.1 mmol/l, or a fasting plasma glucose concentration > 7.0 mmol/l (whole blood > 6.1mmol/l), or two hour plasma glucose concentration > 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT), and the HbA1c of 48 mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes.

Prehypertension is considered to be blood pressure readings with a systolic pressure from 120 mm Hg to 139 mm Hg or a diastolic pressure from 80 mm Hg to 89 mm Hg. Readings greater than or equal to 140/90 mm Hg are considered hypertension.

Nutritional therapies encompass preventive and educational approaches to diet and lifestyle changes including personalized dietary therapy, nutraceutical prescription and lifestyle advice within a functional medicine framework.

Various types of oral nutritional supplements (ONS) are widely used in practice typically macronutrient supplements which may contain vitamins, trace elements and minerals. The use of supplements is believed to confer health benefits, including chronic disease prevention, and thus has lead to the increase daily intake of vitamins and minerals beyond what are obtained from food alone.

Nutraceuticals are products derived from food sources that are sold in the medicinal forms that provide extra health benefits, in addition to the basic nutritional value found in foods. Products may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body.

Nutraceuticals are pharmaceutical products (pills, powders, capsules etc.) containing a concentrated form of a presumed bioactive phytochemical or zoochemical agent (metabolites) from a food. They are used with the purpose of enhancing health in dosages that exceed those which could be obtained from normal foods.

These metabolites have low potency as bioactive compounds when compared to pharmaceutical drugs, but since they are consumed frequently and in significant amounts as part of the diet, they may have significant long-term physiological effects.They differ from another group of products classified as functional foods which are whole foods or foods which contain or maybe fortified/enriched with bioactive agents that is believed to have a potentially beneficial effects on health. The term nutraceutical, coined from the terms nutrition and pharmaceutical has no legal definition. Legislature in most countries categorises nutraceuticals as dietary supplements and therefore, regulation, is not as stringent as for drugs. Nutraceuticals are therefore, widely available and minimally monitored.

However, there is inadequate policy on the use of oral nutritional supplements or vitamin-mineral supplements or nutraceuticals as a complement in the treatment of hypertension and diabetes. There is little rigorous scientific information available to guide in selecting the types and dosages of supplements to be used for disease prevention and complementary to their treatment for hypertension and DM.

Therefore, this HTA is conducted to review the evidences on the efficacy, safety, cost effectiveness and organizational aspects of oral nutritional supplements or vitamin-mineral supplements or nutraceuticals as a complement for diabetes and hypertension.

## Policy Question

a) Should oral nutraceuticals be recommended as a complementary therapy in the treatment of diabetes and hypertension?

b) Should oral nutraceuticals be recommended as a supplement in the pre-diabetes and pre-hypertension?

## Objectives

1. To undertake a systematic review on the effectiveness or efficacy of using ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

2. To assess the safety and cost effectiveness of ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

## Methods

Major electronic databases such as Medline, Embase, Pubmed, EBM reviews, HTA databases, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review were searched up to November 2012. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. The search was limited to publication year from 2000-2012. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals.Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force and data were extracted and narratively presented.

## Results and conclusion

Twenty - one studies were included in this review, where five of the studies were systematic reviews with/ without meta-analysis, fifteen RCT's and one single blind clinical trial. Two of the RCT's included safety.

## I Diabetes

### Efficacy / effectiveness of nutraceutical therapy as a complement for diabetes treatment

#### *Fish oil (EPA & DHA)*

- There was good level of evidence to suggest that Fish oil (EPA & DHA) for type 2 diabetics did not result in any statistically or clinically significant effect for fasting glucose, HbA1c, total cholesterol, or HDL cholesterol. One RCT on thirty four subjects showed that six weeks supplementation with EPA & DHA improved postprandial macrovascular and microvascular function suggesting a protective vascular effect of EPA & DHA. However, further long-term, large-scale studies are warranted to establish this effect.

#### *Bitter melon*

- There was fair to good level of evidence to show that bitter melon for type 2 diabetics had no significant change in blood sugars levels and also no statistically significant difference in the glycaemic control compared to placebo.

#### *Chromium supplementation*

- There was good level of evidence to suggest that for type 2 diabetic patients, chromium supplementation (brewer's yeast 1.28–400 µg/day or Chromium picolinate 60–1,000 µg/day) improved glycosylated hemoglobin levels and fasting glucose but not lipids. However, future studies are needed before definitive claims can be made about the effect of chromium supplementation.

#### *Vitamin C*

- There was good level of evidence to suggest that high-dose oral vitamin C therapy is ineffective at improving endothelial dysfunction and insulin resistance in Type 2 diabetes.

#### *Vitamin C and E*

- It was found that combined treatment with vitamin C and E in pharmacological doses lowers the albumin excretion rate (AER) in Type 2 diabetic patients with micro/ macroalbuminuria. Further long-term, large-scale studies are warranted to provide evidence of effectiveness on using such treatment modality.

- For type 1 pregnant diabetes patients, combined supplementation with vitamin C and E showed no statistically differences between vitamin and placebo groups in the rates of pre-eclampsia, for any clinical neonatal outcome including fetal malformation, fetal loss, infant death, or miscarriage.

#### *Vitamin E*

- There is good level of evidence that 400 IU vitamin E only benefit in subgroup but not all diabetes patients such as DM type 2 with HP 2-2 genotype, where supplementation results in reduction of MI, stroke and CVS mortality.

- In one RCT, short term daily oral supplementation in 41 young type-1 diabetes, with vitamin E (1,000 IU for three months) improves endothelial vasodilator function (EVF) in both the conduit and resistance of the vessels.

***Acetyl-L-Carnitine***

- There was good level of evidence to suggest that 500mg and 1,000mg of acetyl-L-carnitine was found to be efficacious in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with diabetic neuropathy. Future trials are needed to establish such beneficial effects.

***Alpha lipoic acid***

- It was found that supplementation with the oral or intravenous administration of at least 600 mg per day with alpha lipoic acid to diabetic patients resulted in a reduction in the Total Symptom Score (TSS) for pain, burning, paresthesia and numbness but when compared to controls, the reduction in TSS was actually less than the clinically relevant threshold of 30%. Also heart rate and rhythm disorders were observed significantly more frequently in patients treated with alpha lipoic acid compared to patient treated with placebo.

***Cinnamon***

- The results of trials on cinnamon were inconclusive as some showed beneficial effects but others don't. Further trials are needed to establish the beneficial effect of this nutraceutical.

**Fenugreek**

- There was fair level of evidence to suggest that fenugreek 25gm to 100gm/day given to newly diagnosed type 2 diabetes patients may be able to reduce FBG levels and cholesterol level in these patients. However a more robust prospective study is warranted to establish this effect.

***Thiamine***

- In a pilot study on type 2 diabetic patients with microalbuminuria, supplementation with high-dose thiamine (300mg.) produced a regression of urinary albumin excretion (UAE) suggesting that thiamine supplements at high dose may provide improved therapy for early-stage diabetic nephropathy. However, more trials are needed to establish this effect.

***Safety profile of using nutraceutical therapy as a complement to the treatment of diabetes***

- There was good level of evidence to suggest that supplementation with B vitamins containing folic acid (2.5 mg/d), vitamin B6 (25 mg/d), and vitamin B12 (1 mg/d) to T1DM and T2DM patients with diabetic nephropathy and stages 1 to 3 chronic kidney disease, resulted in a greater decrease events in GFR and also increase events in MI and stroke. Therefore, caution should be taken when giving high doses of vitamin B to diabetic patients.

## II Hypertension

*Efficacy / effectiveness of nutraceutical therapy as a complement for hypertension treatment*

***L-arginine***

- There was good level of evidence to suggest that 4 to 24 gm. /day oral L-arginine supplementation significantly lowers both systolic and diastolic BP

***Calcium***

- There was good level of evidence to suggest that adequate intake of calcium (0.5 to 2 gm. /day) in the form of calcium gluconate, calcium carbonate or calcium citrate may be recommended for the prevention of hypertension. Supplementation of calcium during pregnancy reduced the risk of preeclampsia, risk of maternal mortality/severe morbidity and there was also a reduction in the risk of pre-term birth.

### *Magnesium*

- There was good level of evidence to suggest that there is a dose-dependent BP reduction from magnesium supplementation. However, further trial with adequate sample power will be required to confirm the relation between magnesium and hypertension.

### *Garlic*

- There was good level of evidence to suggest that garlic preparations (600–900 mg per day, providing potentially 3.6–5.4 mg of allicin) may be useful in reducing blood pressure in individuals with hypertension.

*Safety profile of using nutraceutical therapy as a complement to the treatment of hypertension*

### *Combined vitamin C (1000 mg) and E (400 IU)*

- There was good level of evidence to suggest that supplementation of combined vitamin C (1000 mg) and E (400 IU) to pregnant patients with hypertension showed no significant reduction in the rate of preeclampsia compared to placebo. Premature rupture of the membranes was more frequently observed in the study vitamin group. Among patients without chronic hypertension, there was a slightly higher rate of severe preeclampsia in the study group compared with placebo. Hence, Vitamins C and E supplementation in this dose combination may be associated with an increased risk of premature rupture of the membranes (PROM) and preterm premature rupture of the membranes (PPROM).

## Recommendations

### I Diabetes

### *Nutraceutical therapy as a complement for diabetes*

Based on the above review:

- Complementary treatment with fish oil, bitter melon and vitamin C, Combination of Vitamin C & E and high doses of B vitamins appeared to offer no benefit in terms of glycaemic control as reflected in HbA1c level, postprandial blood glucose and fasting blood glucose as reported in some studies.
- The effect of cinnamon on fasting blood glucose level and HbA1c was inconclusive
- The use of high doses of B vitamins (containing 2.5 mg/d of folic acid, 25 mg/d of vitamin B6, and1mg/d of vitamin B12) on participants with diabetic nephropathy and stages 1 to 3 chronic kidney disease resulted in a greater decrease in GFR and an increase in MI and stroke and suggesting harm to these patients.
- Vitamin E supplementation was inconclusive to reduce the composite outcome of myocardial infarction, stroke, and cardiovascular death. A large subgroup of DM individuals with the Hp 2-2 Genotype may potentially derive cardiovascular benefit from Vitamin E supplementation.

Hence, these nutraceuticals (fish oil, bitter melon, high dose vitamin C, and combination of vitamin C & E, high doses of vitamin B6, B12, cinnamon and Vit E) cannot be recommended as a complement therapy for diabetes until futher scientific evidence is obtained to establish their effectiveness and safety.

**Based on the above review:**

- Fenugreek, chromium supplementation (brewer's yeast and chromium picolinate) appears to have significant effects on fasting glucose.
- High dose thiamine seems to lower albumin excretion rates in Type 2 diabetic patients with micro/macroalbuminuria.
- Acetyl-L-carnitine may have potential in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy. It also reduces oxidized LDL cholesterol levels in patients with type 2 diabetes.
- Alpha lipoic acid 600 mg per day supplementation may have potential in alleviating symptoms, particularly pain. However, it should be used with caution as adverse events such as heart rate and rhythm disorders were observed.

Therefore, more research with larger, high quality randomised clinical trials are warranted to provide more conclusive scientific evidence on the long term safety and effectiveness of nutraceuticals such as fenugreek, chromium, Vitamin E, thiamine, Acetyl-L-carnitine and Alpha lipoic acid before these can be recommended as a complementary therapy for diabetes in Malaysia.

## II Hypertension

### *Nutraceutical therapy as a complement for hypertension*

Based on the above review:

- Vitamins C (1000 mg) and E (400 IU) supplementation in this dose combination may be associated with an increased risk of premature rupture of the membranes (PROM) and preterm premature rupture of the membranes (PPROM).

Therefore, this combination **is not recommended for pregnant hypertensive** patients.

- An adequate intake of calcium in the form of calcium gluconate, calcium carbonate or calcium citrate has been shown to reduce both systolic and diastolic BP. Calcium supplementation during pregnancy reduced risk of preeclampsia, risk of maternal mortality/severe morbidity, reduction in risk of pre-term birth.

Therefore, calcium in the form of calcium gluconate, calcium carbonate or calcium citrate may be recommended for the prevention of hypertension in appropriate therapeutic doses.

- Oral L-arginine supplementation has been shown to lower both systolic and diastolic BP.
- Garlic preparations may have the potential in reducing blood pressure in individuals with hypertension.
- There was also a dose-dependent BP reduction from magnesium supplementation.

However, since the study trials were small, therefore, more research with larger, high quality randomised clinical trials are recommended to provide more conclusive scientific evidence before oral L-arginine, garlic preparations and magnesium supplementation can be established as nutraceuticals to be used as a complement therapy for hypertension.

## III Other Concerns

Commercially available nutraceutical products are not standardized and vary in the content of active ingredients. Issues such as bioavailability, bioactivity of metabolites, dose/response and toxicity of bioactive compounds need to be considered when presented as nutraceuticals. Interaction of these nutraceuticals with other drugs or between different nutraceuticals when taken as a cocktail of supplements are areas of concern and more research are needed to provide solid evidence on these issues.

Sufficient legislative safeguards are essential on the use of nutraceuticals in Malaysia. Until further evidence is available, health professionals should be alerted to the possibility of adverse effects of nutraceuticals, the potential for harmful interactions with other medications and nutritional imbalances due to overuse. In order to have scientific knowledge about the nutraceuticals, public should be educated, where recommended daily doses of these nutraceuticals should be known by each consumer. Hence, large, well designed, randomized, placebo-controlled studies, powered to detect differences in clinical events, are needed to examine any potential role of nutraceutical therapy as an adjunct to existing treatment paradigms.

### *Current international regulatory status of nutraceuticals and functional foods:*

***Japan**:* It was the first to introduce the term "functional foods" in early 1980s. After lengthy consultation the legislation "*tokutei hokenyo shokuhin*", which in English was translated as "foods for specified health use" (FOSHU), was introduced in 1991. The process of getting an FOSHU status is complex and involves 3-steps-development of a product using approved ingredients, conduct clinical trial and submit documentation to the Ministry of Health and Welfare for evaluation and approval.

***United States of America:*** There is no legislative definition for Functional Foods in the US. In the USA the US Federal Food, Drug and Cosmetics (FD&C) and US Federal Trade Commission (FTC) have jurisdiction over foods. Under a memorandum of understanding (MOU), FD&C is responsible for labelling of product, whereas FTC is responsible for food advertising. Sales, development and health claims of foods fall under three major acts. They are: Nutrition labelling and Education Act (NLEA) of 1990; Dietary Supplementary Health and Education Act (DSHEA) of 1994 and Food and Drug Administration of Modernization of 1997.

***Canada**:* As per current Canadian Food and Drug Acts any food that claims to have health benefits would fall into drug category. In the *Policy Paper on Nutraceuticals/Functional Foods and Health Claims on Food*, Health Canada made the policy decision that the structure/function and risk reduction claims for foods should be permitted while all others claiming to cure, treat, mitigate or prevent illness should be regulated as drugs.

***The European Union**:* Until recently regulating the dietary supplement has been left with each member country. After a lengthy, highly divisive consultative process, the Food Supplement Directive (Directive 2002/46/EC) was signed into law on July 12, 2002. This legislation harmonises vitamin and mineral regulations in all member countries, the 13 countries that have applied for admission. This legislation establishes a list of minerals and vitamins that can be marketed in all member states, but will prohibit sale of a large number of nutrients currently sold in the United Kingdom and other European countries, because they are not in the list.

***Sweden**:* Since 1990, in consultation with the Swedish Nutrition Foundation (SNF), Sweden has allowed the use of health-related claims in the labelling and manufacturing of foods. In 2001, Sweden extended this generic claim to include product-specific physiological claims under PARNUT. This involves developing a Code with a consensus between industries, consumer groups, researchers and regulators.

***Israel**:* The Food and Nutrition Service of Israeli's Health Ministry is proposing amendments to its existing food regulations which would allow manufacturers of certain food and supplement products to make claims about health benefits of their products. The amendments are an extension of the rules of the US Food and Drug as listed in Dietary Supplementary Health and Education Act (DSHEA ) and Food and Drug Administration Modernization Act (FDAMA).

There was no retrievable scientific evidence on the cost, cost effectiveness, organizational, social and cultural aspects of nutraceuticals to complement therapy for diabetes and hypertension.

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# ABBREVIATIONS

| | |
|---|---|
| **AER** | Albumin excretion rate |
| **ALC** | Acetyl L- carnitine |
| **BP** | Blood pressure |
| **CAM** | Complementary and alternative medicine |
| **CI** | Confidence Interval |
| **CV** | cardiovascular |
| **DM** | Diabetes mellitus |
| **DSHEA** | Dietary supplementary Health and Education Act |
| **EVF** | Endothelial vasodilator function |
| **FBF** | Forearm blood flow |
| **FBS** | Fasting blood sugar |
| **FBG** | Fasting blood glucose |
| **FD&C** | Federal Food, Drug and Cosmetics |
| **FMD** | Flow mediated dilatation |
| **FTC** | US Federal Trade Commission |
| **GFR** | Glomerular filtration rate |
| **HbA1c** | Glycated hemoglobin; Glycosylated haemoglobin |
| **HDL** | High-density lipoprotein |
| **HDLC** | High-density lipoprotein cholesterol |
| **HR** | Hazard ratio |
| **HTA** | Health Technology Assessment |
| **LDL** | Low-density lipoprotein |
| **LDLC** | Low-density lipoprotein cholesterol |
| **MI** | Myocardial infarction |
| **MOU** | Memorandum of understanding |
| **ONS** | Oral Nutritional Supplements |
| **OR** | Odds ratio |
| **PARNUT** | Foods for Particular Nutritional Use |
| **PROM** | Premature rupture of the membranes |
| **PPROM** | Preterm premature rupture of the membranes |
| **PPS** | Post prandial plasma glucose |
| **RCT** | Randomised control trials |
| **RH** | Reactive hyperaemia |
| **SAC** | Systemic arterial compliance |
| **SBP** | Systolic blood pressure |
| **SD** | Standard deviation |
| **SE** | Standard error |
| **SNP** | Sodium nitroprusside |
| **T&CM** | Traditional and Complementary Medicine |
| **TG** | Triglycerides |
| **TLC** | Total cholesterol |
| **T2DM** | Type 2 Diabetes mellitus |
| **TSS** | Total symptom score |
| **UAE** | Urinary albumin excretion |

# CHAPTER 1: BACKGROUND

## Description of health problem

The study of nutrition was initiated as early as the 18th century and by the early 20th century, scientists had found that diseases such as beri beri, rickets, scurvy, and pellagra were associated with certain diets. By 1912, a chemist had found a substance (vitamin B1) that actually prevented beri beri, and he named it "vitamin." Later it was found that these diseases were caused by the lack of specific nutrients namely vitamin B1 (thiamine), vitamin D, vitamin C and vitamin B3 (niacin). Researchers and scientists continue to find out more about how individual nutrients can help prevent and treat diseases.

Globally, magnitude of non-communicable diseases has been rapidly growing and constitutes one of the major public health challenges. In 2008, 63% of global deaths were due to non-communicable diseases. In the United States (2008), 68 million populations were estimated to have hypertension[1], which increases the risk for the leading causes of death, heart disease and stroke. Similarly, Diabetes Mellitus (DM) epidemic is accelerating in the developing world, with an increasing proportion of affected people is in the younger age groups. In Malaysia, the prevalence of both hypertension and Type 2 DM (T2DM) is also rising as demonstrated in the National Health and Morbidity Survey 2011 whereby hypertension among adult of 18 years and above was 32.7% and T2DM of 15.2%.[2] There was an increasing trend in prevalence with age from 8.1% for hypertension and 2.1% for diabetes in the 18-19 years old age group reaching a peak of 74.1% for hypertension and 36.6% for diabetes among 65-69 year olds.[2] These chronic diseases have common risk factors and underlying pathologic mechanisms that may be modified by nutrients.

According to WHO criteria, prediabetes is considered to be readings with: a)Fasting blood sugar (glucose) level of: 110 to 125 mg/dL (6.1 mmol/l to 6.9 mmol/l ), whilst ADA criteria suggests 100 to 125 mg/dL (5.6 mmol/l to 6.9 mmol/l ). For prediabetics, two hour glucose tolerance test reading showed the blood sugar level of 140 to 199 mg/dL (7.8 mmol/l to 11.0 mmol/l ) and the HbA1c is in the range of 5.7 to 6.4 percent.

Prehypertension is considered to be blood pressure readings with a systolic pressure from 120 mm Hg to 139 mm Hg or a diastolic pressure from 80 mm Hg to 89 mm Hg. Readings greater than or equal to 140/90 mm Hg are considered hypertension.

Nutritional therapy encompasses a broad range of options from changing one's diet, lifestyle changes/ modifications programme and nutritional supplementation with vitamins and minerals in prescribed doses. Dietary supplements are defined in the United States Dietary Supplement Health and Education as any product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following ingredients: a mineral; a vitamin, a herb or other botanical, an amino acid, a supplement used by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any ingredient described (Dietary, 1994)[3].

Various types of oral nutritional supplements (ONS) are used in practice typically macronutrient supplements which may contain vitamins, trace elements and minerals. The use of supplements believed to increase daily intake of vitamins and minerals beyond what is obtained from food alone and may confer health benefits, including chronic disease prevention. [4]

It was estimated 40% of people consume nutritional supplements with major type of nutritional supplement appears to be combination of vitamin/mineral supplements.[5, 6 7]

Basically to define, nutraceutical is a marketing term developed for nutritional supplement that is offered with the objective to augment health, treat, or prevent specific disease condition by modulating vitality.[8] Nutraceuticals are products derived from food sources that are sold in the medicinal forms that provide extra health benefits, in addition to the basic nutritional value found in foods. Products may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body. Hence a "nutraceutical" is any substance that may be considered a food or part of a food and provides medical or health benefits, encompassing, prevention and treatment of diseases.[9] Nutraceuticals are sometimes referred as "*functional foods*" because when functional food aids in the prevention and/or treatment of disease(s)/ disorder(s) other than deficiency conditions like anemia it is called a "nutraceutical".[10] Thus, nutraceuticals differ from dietary supplements in the following aspects: nutraceuticals must not only supplement the diet but should also aid in the prevention and/or treatment of disease and/or disorder.[11]

Many industries manufacture and market these nutraceuticals, where the side effects (especially when consumed in large quantities) of these nutraceuticals are not clearly reported or often have unproven benefits. In order to have access to scientific knowledge about the nutraceuticals, the public should be educated, by making the recommended daily doses of these nutraceuticals available to the consumers.[12]

## Current service provision

Currently in Malaysia there is inadequate policy on the use of ONS or vitamin-mineral supplements or nutraceuticals as a complement in the treatment of hypertension and diabetes. There is no national standard or holistic approach using nutraceuticals in management of patients with chronic diseases especially diabetes or hypertension. There is little rigorous scientific information available to guide in selecting the types and dosages of supplements to be used for disease prevention and complementary to their treatment for hypertension and DM.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, cost effectiveness and organizational aspects of oral nutritional supplements or vitamin-mineral supplements or nutraceuticals as a complement for diabetes and hypertension.

## Technical Features

Nutraceuticals are pharmaceutical products (pills, powders, capsules etc.) containing a concentrated form of a presumed bioactive phytochemical or zoochemical agent (metabolites) from a food and used with the purpose of enhancing health in dosages that exceed those that could be obtained from normal foods.[8] These metabolites have low potency as bioactive compounds when compared to pharmaceutical drugs, but since they are consumed frequently and in significant amounts as part of the diet, they may have significant long-term physiological effects.[9] They differ from another group of products classified as functional foods which are whole foods or foods which contain or maybe fortified/enriched with bioactive agents that have a potentially beneficial effects on health.[8] The term nutraceutical, coined from the terms nutrition and pharmaceutical has no legal definition.[8]. Legislature in most countries categorises nutraceuticals as dietary supplements and therefore, regulation, is not as stringent as for drugs.[8, 9] Nutraceuticals are therefore, widely available and minimally monitored.[8]

# CHAPTER 2: DEFINITION OF POLICY QUESTION AND OBJECTIVES

## Policy Question

a) Should oral nutraceuticals be recommended as a complementary therapy in the treatment of diabetes and hypertension?

b) Should oral nutraceuticals be recommended as a supplement in the pre-diabetes and pre-hypertension?

## Overall aims and objectives of the assessment

This project aims to provide evidence based guidance on the use of nutritional therapy (nutraceuticals) as a complement therapy in the management of diabetic and hypertensive patients and ultimately help the Traditional and Complementary Medicine (T&CM) Division identify and guide the T&CM practitioners on the complement management of diabetic and hypertensive patients to be adopted or adapted in Malaysia. In order to do so, certain critical areas of care were identified to be assessed and these objectives were outlined:

1. To undertake a systematic review on the effectiveness or efficacy of using ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

2. To assess the safety and cost effectiveness of ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

These objectives were developed into a series of questions, which were addressed in a review:

a) Is oral nutraceuticals effective as a complementary therapy in the treatment of diabetes and hypertension?

b) Is oral nutraceuticals effective as a complementary therapy in the treatment of gestational diabetes and gestational hypertension?

c) Is oral nutraceuticals effective as a supplement for pre-hypertension and pre-diabetes?

d) Is there any adverse events related to oral nutraceuticals?

e) Is oral nutraceuticals cost-effective compared to usual care?

# CHAPTER 3: METHODS

Methods of the review, analysis and inclusion criteria has been specified in advance and documented in a protocol.

## Search Strategy

The search aimed to systematically identify all literature related to the questions in this review. The last search was conducted in November 2012.

### Sources searched

Eight electronic databases were searched from inception: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); Pubmed; The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases.

In addition to the database searches, articles were identified from reviewing the bibliographies of retrieved articles and hand searching of journals.

### Search terms

A combination of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords free text. Copies of the search strategies used in MEDLINE are included in Appendix ** (these were adapted for use in other databases). The search was limited by including search filters for 'human studies'. The search was also limited to publication year from 2000-2012.

## Inclusion and exclusion criteria

Eligibility assessment was conducted by two reviewers in an unblinded standardised manner independently using these prespecified inclusion and exclusion criteria.

### Inclusion criteria

After discussion with the expert committee, it was agreed that articles were selected for inclusion in this systematic review on the basis of the following criteria:

### Study design

For systematic review on clinical effectiveness, systematic reviews, meta-analysis, randomized controlled trials, non-randomised comparative studies and trials with surrogate end points will be included. Additional studies such as cohort, case control, cross sectional will also be taken into consideration especially if the studies are related to safety or adverse events.

## Population

Subjects with Diabetes Mellitus (Type 1 DM, Type 2 DM, gestational diabetes), subjects with hypertension, pre-diabetes, pre-hypertension

## Intervention

a. Nutraceuticals for hypertension such as:
   i. L. arginine,
   ii. Fish oil (EPA50/DHA20),
   iii. Co-enzyme Q10,
   iv. Vit D3,
   v. Mixed tocopherol (vitamin E),
   vi. Calcium carbonate,
   vii. Magnesium citrate,
   viii. Potassium gluconate

b. Nutraceuticals for diabetes such as:
   i. Fish oil (EPA50/DHA20), fatty acid in specific dosage form
   ii. Garcinia Cambogia (standardized to 60% hydroxycitric acid),
   iii. Bitter melon or bitter gourd (e.g. standardized 10% momordica charantia) in specific dosage form
   iv. Chromium polynicotinate,
   v. D-alpha tocopherol,
   vi. Gamma tocotrienol,
   vii. Vitamin C (ascorbic acid/ascorbate),
   viii. L- carnitine,
   ix. Alpha lipoic acid,
   x. Magnesium citrate,
   xi. Cinnamon ( cinamomum) in specific dosage form
   xii. Fenugreek in specific dosage form
   xiii. Selenium from yeast,
   xiv. Vitamin A (beta-carotene),
   xv. Vitamin B1 (thiamine),
   xvi. Vitamin B12 (cyanocobalamine/ cobalamine),
   xvii. Vitamin B6 (pyridoxine)

### Comparators

a. Placebo

b. Usual care/ standard care

### Outcome

One or more of the following outcome measures were assessed

i. Efficacy of oral nutraceuticals (vitamins/ mineral etc) to reduce diabetes, pre-diabetes, pre-hypertension or hypertension through glycaemic control, HbA1c, systolic, diastolic pressure

ii. Reduction in morbidity related to diabetes, pre-diabetes, pre-hypertension or hypertension with ONS

iii. Reduction in micro-vascular or macro-vascular complications, neuropathy, nephropathy, fetal outcomes with nutraceuticals

iv. All cause mortality and cardiovascular effects

v. Surrogate outcomes or biomarkers

vi. Reduction in diabetes or hypertension, pre-diabetes or pre-hypertension mortality with ONS

vii. Weighted mean differences, adjusted odd ratios (ORs) and relative risks with 95% confidence intervals (CIs) from individual studies

viii. Multivariable adjusted hazard ratios with 95% confidence intervals (CIs) from individual studies

ix. Adverse events, safety

x. Articles from year 2000

### Publication

Full text articles published in English

### Exclusion criteria

i. Animal study

ii. Narrative review

iii. Laboratory study

iv. Non English full text articles

v. Raw food and spices (without specific dosages) is excluded because it is classified under naturopathy

vi. Patients with lifestyle modification/ diet modification, parenteral nutritional supplement.

vii. Articles published before year 2000 on were excluded

### Quality assessment strategy, grading of evidence and conclusion

The validity of the eligible studies was assessed by two reviewers independently using prespecified criteria. For systematic reviews and meta- analysis, the criteria assessed include unbias selection of articles, heterogeneity of the included studies and publication bias. For RCTs, the criteria assessed were sequence generation, allocation concealment, blinding, explanation on loss to follow up, intention to treat analysis and other potential sources of bias such as funding. For non-randomised studies with comparison, the criteria assessed were random selection of participants, prospective or retrospective study, blinding, explanation on loss to follow up, control of confounding factors and other potential sources of bias. For economic evaluation, we used two steps to evaluate the risk of bias. First we used the same criteria as RCTs and non-RCTS, then we appraised following Critical Appraisal Skill Programs checklist for economic evaluation.

The quality of the evidence was later graded according to US/Canadian Preventive Services Task Force grading system (see Appendix 5).[8] Caution in interpretation should be encouraged since the grades chosen to indicate the strength of evidence cannot be interpreted as the ultimate truth. It is also important to note that when scientific evidence is concluded as being insufficient, this does not necessarily mean that the given method has no effect.

### Data extraction strategy

Data from included studies were extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements were resolved through discussion. A third person, whose decision is final, will be consulted if disagreements persist after discussion.
Information was extracted from each included trial on (1) characteristics of trial participants (2) the trials inclusion and exclusion criteria (3) type of intervention (4) type of control used (5) outcome measures.

### Data synthesis

All the data extracted were summarized in evidence table. The evidence was presented to a multidisciplinary expert committee member. Data were assessed for suitability for pooling with regards to the intervention, study design, populations, comparators and outcome. Due to methodological and clinical heterogeneity of the studies, a narrative synthesis was used.

The overall search results were presented in Chapter 4. The detailed results were presented in Chapters according to the research questions, namely

Chapter 5: Nutritional therapy as a complement for diabetes, gestational diabetes and pre-diabetes.

Chapter 6: Nutritional therapy as a complement for hypertension, gestational hypertension and pre-hypertension.

# CHAPTER 4: OVERALL SEARCH RESULTS

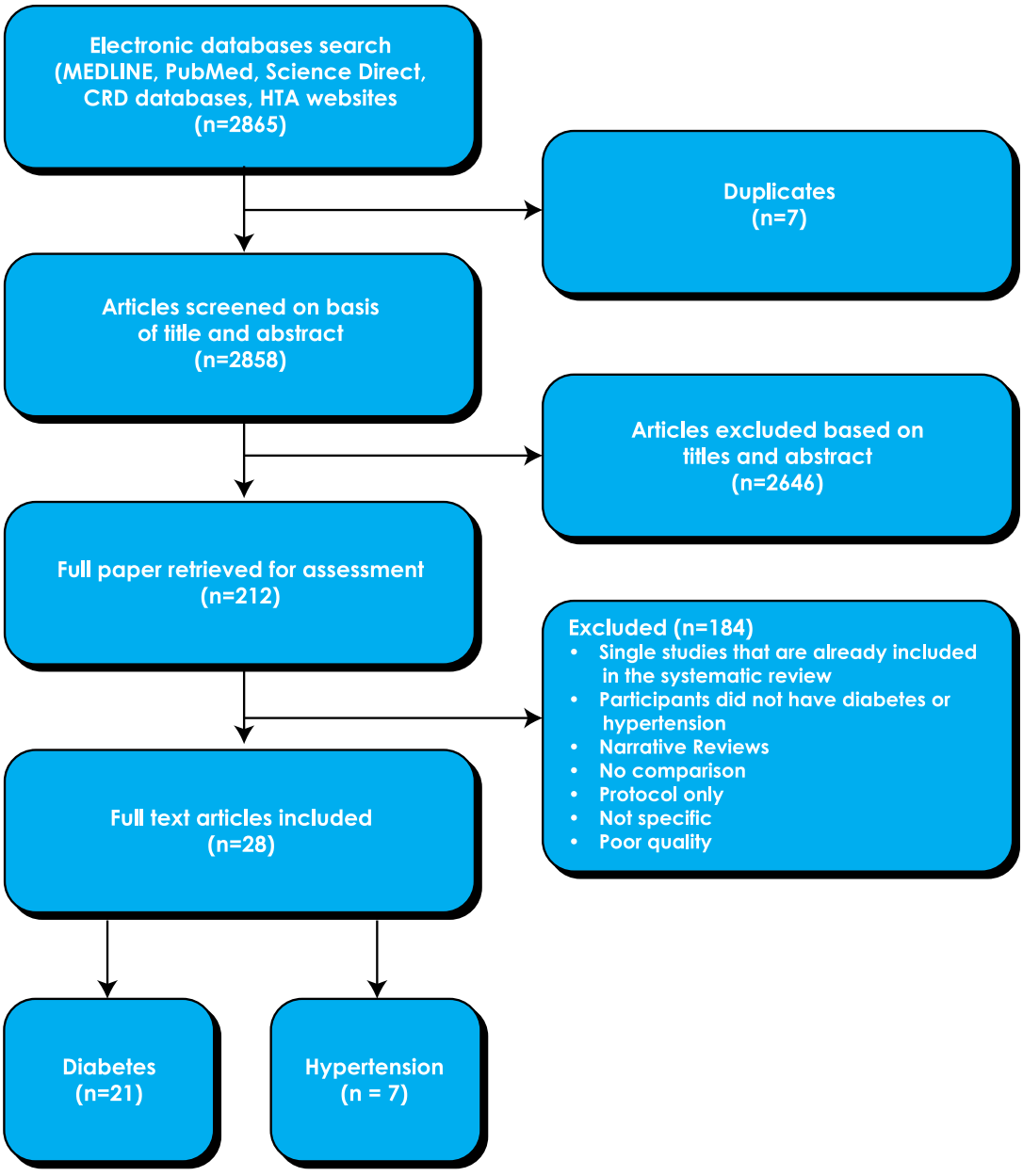
The electronic searches identified 2865 articles. Out of these 2865 articles, seven were duplicates. Two reviewers screened 2858 titles and abstracts. A total of 212 full text articles were retrieved for assessment. Twenty-eight articles met our inclusion and exclusion criteria.

A flow diagram showing the number of articles identified, retrieved and included in the review is presented in Figure 1.

The evidence tables of these studies were presented in Appendix 6. The excluded studies were listed in Appendix 7.

The characteristics of included studies are discussed in the relevant chapters.

**Figure 1. Flow chart of study selection**



# CHAPTER 5: NUTRITIONAL THERAPY AS A COMPLEMENT FOR DIABETES

## INTRODUCTION

Diabetes Mellitus and its associated complications are considered among the leading causes of morbidity and mortality, and therefore constitute a major public health problem.[13] Diabetes, like most chronic health conditions, not only places substantial economic burdens on society as a whole but also imposes considerable economic burdens on individual patients and their families. In US alone the estimated expenditures for health care for people with diabetes totaled $85.7 billion (11.9% of total health care expenditures) in 1992.[14] Although there is widespread use of herbal dietary supplements that are believed to benefit type 2 diabetes mellitus, few have been proven to do so in properly designed randomized trials.

In the past, diabetic management simply meant managing high blood glucose levels; however that is simply not good enough. The three key areas in this new paradigm of diabetic management, proposed by Dr. Ralph DeFronzo at the 2008 American Diabetes Association meeting in San Francisco, are: managing hyperglycemia, managing insulin resistance and Beta-cell preservation. Educating the pre-diabetic, diabetic patients and encouraging them to make healthy lifestyle changes is just as important as prescribing drug therapy.[15, 16, 17, 18]

The use of complementary and alternative medicines (CAM) such as plant-based medicines and dietary supplements for the treatment of diabetes is widespread and increasingly practiced worldwide.[19] Studies on the simultaneous use of herbal medicines with the conventional therapy for management of diabetes are limited. The range of nutraceutical compounds that might have potential efficacy in this regard continues to expand.[20, 21] Several areas of concern exist with use of dietary supplements and nutraceuticals in patients with diabetes includes product standardization, optimal dosing regimen, potential side effects, drug interactions, and need for evidence based indications.[20, 21] The purpose of this review is to discuss these issues and provide evidence on the use of nutraceuticals to complement the treatment of diabetes.

## CHARACTERISTICS OF INCLUDED STUDIES

### Study design

Twenty - one studies were included in this review, where five of the studies were systematic reviews with/ without meta-analysis, fifteen RCT's and one single blind clinical trial. As for the RCT's two of the studies were on safety.

### Participants

Most of the studies included patients with type 1 or type 2 diabetes. There was only one study on pre-diabetic patients and no study on gestational diabetic patients.

### Intervention

Most of the studies were using nutraceuticals with usual care for the intervention group. The nutraceuticals included in the studies were fish oil, bitter melon (bitter gourd), chromium alpha tocopherol, Vitamin C, L- carnitine, alpha lipoic acid, magnesium, cinnamon,fenugreek ,selenium, vitamin B1 (thiamine), vitamin B12 (cyanocobalamine/ cobalamine), vitamin B6 (pyridoxine)

### Comparators

The comparators were patients on usual care with their usual medication, diet or lifestyles.

### Outcome measures

The outcome measures assessed in the studies included: Efficacy/ Effectiveness of nutraceuticals to reduce diabetes, pre-diabetes and gestational diabetes through glycaemic control, HbA1c, reduction in morbidity related to diabetes, pre-diabetes, gestational diabetes: reduction in micro-vascular or macro-vascular complications, neuropathy, nephropathy, fetal outcomes, all cause mortality and cardiovascular effects: surrogate outcomes or biomarkers, weighted mean differences, adjusted odd ratios (ORs) and relative risks with 95% confidence intervals (CIs) from individual studies, multivariable adjusted hazard ratios with 95% confidence intervals (CIs) from individual studies, adverse events or safety.

## EFFICACY/ EFFECTIVENESS

### Fish oil

(Subjects: Type 2 diabetic patients)

Montori VM et al did a systematic review whereby a total of 823 subjects were included in the 18 trials.[22] Most participants had type 2 diabetes of 5–10 years' duration and were treated with diet or oral hypoglycemic agents. The dose of fish oil ranged from 3 to 18 g (1.08–5.2 g EPA and 0.3–4.8 g DHA). The fish oil was usually given in capsules with the exception of 1 study, in which a liquid form was used. The dose of placebo was matched to the dose of fish oil. The placebo used was a vegetable oil with the exception of 1 study that used a saline solution. No statistically significant effect was observed for fasting glucose, HbA1c, total cholesterol, or HDL cholesterol.

- The overall weighted mean difference (-) for fasting glucose was 0.26 mmol/l (95% CI; -0.08 to 0.60) and for HbA1c was 0.15% (95% CI; -0.08 to 0.37).
- The overall weighted mean difference (-) for total cholesterol was 0.007 mmol/l (95% CI; -0.13 to 0.15).
- A statistically significant increase in LDL cholesterol was especially noted in the studies recruiting hypertriglyceridemic subjects and using the highest doses of fish oil. Meta-analysis of pooled data demonstrated a statistically significant effect of fish oil on lowering triglycerides (-0.56 mmol/l [95% CI; -0.71 to -0.41]) and raising LDL cholesterol (0.21 mmol/l [95% CI; 0.02 to 0.41]).

- For the study by Pelikanova et al using normal saline as the placebo; the overall weighted mean difference showed reduction in fasting blood glucose of 1.20mmol/l (95% CI; -0.59 mmol/l to 2.99 mmol/l) and for HbA1c it was 0.9% (95% CI; 0.015% to 01.785%).

Hence, fish oil supplementation in type 2 diabetes lowers triglycerides, raises LDL cholesterol, and has no statistically significant effect on glycemic control. Trials with better clinical end points are needed.

Stirban A et al. did a randomized study on thirty-four subjects with Type 2 Diabetes aged 37–70 years old, with no history of major cardiovascular events or a surgical or interventional history within the previous 6 months in Germany.[23] Patients were given 2 capsules of the study medication which consisted of capsules weighing 1 g containing omega-3 acid ethyl ester (purified EPA/DHA [termed n-3 FAs]) or placebo capsules containing olive oil that were externally identical and followed up for 6 weeks. Macro vascular (brachial ultrasound of flow-mediated dilatation; FMD) and microvascular [laser-Doppler measurements of reactive hyperemia (RH) of the hand] function at fasting and 2, 4, and 6 h after a highfat meal (600 kcal, 21 g protein, 41 g carbohydrates, 40 g fat) were measured. The results were:

- Fasting vascular function remained unchanged after n-3 FAs and placebo.
- After placebo supplementation, a significant decrease in postprandial FMD occurred (maximum decrease in FMD was at 4 h: 38% decrease from fasting value), while supplementation with n-3 FAs resulted in a significant decrease in postprandial FMD (FMD decreased by 13% from the fasting value at 4 h)
- RH remained unchanged after placebo but it improved significantly after n-3 FA supplementation (maximum increase was at 2 h: 27%).
- Fasting triglycerides and other variables did not change significantly with the treatment (n-3 FAs): Hb A1C (7.1 ± 0.2% treated group compared with 7.1 ± 0.2% placebo group), total cholesterol (184 ± 6 mg/dL treated group compared with 190 ± 6 mg/dL placebo group), LDL cholesterol (112 ± 5 mg/dL treated group compared with 113 ± 5 mg/dL placebo group), HDL cholesterol (46 ± 2 mg/dL treated group compared with 47 ±2mg/dL placebo group.

In subjects with type 2 diabetes mellitus, 6 weeks of supplementation with n-3 FAs improved postprandial microvascular function which suggest a protective vascular effect of n-3 FAs.

### Bitter melon

(Subjects: Type 2 diabetic patients)

Momordica charantia, known as bitter melon or gourd, is widely consumed as a vegetable and bitter flavoring in cookery, especially in Asian countries such as China and India. Consumption of momordica charantia has been linked to a variety of health-promoting benefits, including lowering blood glucose in hyperglycemic subjects.

John AJ et al conducted a study in a tertiary care 1800-bed teaching hospital in south India on mild to moderate type 2 DM patients.[24] Patients were randomized to receive either bitter gourd tablets (26 subjects) or placebo (24 subjects). The bitter gourd tablets were made from shade dried powdered fresh whole fruit. The average sized fruit weights around 5 gm when dried. Each tablet contained 1 gm of dried fruit and each patient received 2 tablets thrice daily, after meals. Riboflavin was given as placebo. All patients were asked to continue their routine anti diabetic treatment, which included dietary modification and oral hypoglycemic agents such as sulfonylureas and biguanides. The mean values of FBS, PPS and fructosamine after 2 and 4 weeks showed no significant change.

- The FBS was 150.1±26.9 mg/dl at baseline and 150.0±35.3 mg/dl after 4 weeks in the treatment group while it was 155.8±25.0 mg/dl at baseline and 150.7±35.4 mg/dl after 4 weeks in the placebo group.
- The PPS was 264.4±32.8 mg/dl at baseline and 230.4±61.2 mg/dl after 4 weeks in the treatment group while it was 253.8±29.4 mg/dl at baseline and 257.6±62.9 mg/dl after 4 weeks in the placebo group.
- The Fructosamine value was 350.8±56.8 mg/dl at baseline and 319.1±60.7 after 4 weeks in the treatment group while it was 349.1±62.0 a mg/dl at baseline and 333.9±64.1 mg/dl after 4 weeks in the placebo group.

The present study showed no significant change in blood sugars or fructosamine levels in either treatment or placebo group. The mean drop in blood sugars and serum fructosamine levels in both groups over time was also not significant.

In a systematic review by Ooi CP et al, the authors assessed the effects of mormodica charantia for type 2 diabetes mellitus.[25] Four randomised controlled trials with up to three months duration and investigating 479 participants met the inclusion criteria. Primary outcomes were: Fasting blood glucose levels (FBG), Glycosylated haemoglobin A1c (HbA1c) and adverse effects (e.g. hypoglycaemia) The results showed that:

- There was no statistically significant difference in the glycaemic control with momordica charantia preparations compared to placebo.
    - Change in HbA1c 0.22% [95% CI, -0.36% to 0.80%] as shown in the study by Dans et al 2007
    - Change in fasting blood glucose: 0.66 mmol/L [95% CI; -1.69 to 3.01 mmol/L] as shown in the study by Dans et al 2007,while in the study by John et al 2003, the change in fasting blood glucose was -0.70 mg/dL [95% CI; -22.40 to 21.00 mg/dL ]
    - Postprandial blood glucose: -27.20 mg/dL [95% CI; -65.33 to 10.93 mg/dL] as shown in the study by John et al 2003
    - Change in serum fructosamine: mean difference was -14.80 mol/ L[95% CI; -53.19, 23.59 mol/ L ] as shown in the study by John et al 2003

- When momordica charantia was compared to metformin there was also no significant change in reliable parameters of glycaemic control

- Change in serum fructosamine: 6.60 mol/L [ 95% CI; -9.64 to 22.84 mol/L ] as shown in the study by Fuangchan et al 2011

- Purificacion et al.,2007 reported that the effect of the momordica charantia leaf preparation intervention was comparable with the control intervention of low dose glibenclamide tablets (2.5 mg twice a day).

- No serious adverse effects were reported in any trial. No trial investigated death from any cause, morbidity, health-related quality of life or costs

The above reviews suggested that there are insufficient evidences to suggest beneficial effects of momordica charantia for type 2 DM due to small sample size and quality of the studies. Further studies are therefore required to address the issues of standardization and the quality control of the momordica charantia preparations. For medical nutritional therapy, further trials evaluating the effects of momordica charantia are needed before making any recommendations in clinical practice.

### Chromium

(Subjects: Type 2 diabetic patients)

In a systemic review done by Balk EM et al., to assess the effects of chromium supplementation on glucose metabolism and lipid levels, 41 studies met the inclusion criteria, almost half of which were of poor quality and included 1,198 participants.[26] Almost all participants had diabetes type 2 although in three studies this was unclear. Four different chromium formulations were used as intervention: brewer's yeast (1.28–400 µg/day, 10 studies), chromium chloride (50–600 µg/day, 15studies), chromium nicotinate (200–800 µg/day, 5 studies) and chromium picolinate (60–1,000 µg/day, 15 studies). One study did not describe the chromium formulation (400µg/day). Study duration ranged from 3 weeks to 8 months. Results were shown below:

- Among participants with type 2 diabetes, chromium supplementation improved glycosylated hemoglobin levels by-0.6% (95% CI; -0.9% to -0.2%) and fasting glucose by -1.0 mmol/l (95% CI; -1.4 to - 0.5 mmol /l) but not lipids.

- The overall estimate for the effect of supplementation with brewer's yeast on fasting glucose was statistically significant, -1.1 mmol/l (95% CI; -1.6 to -0.6 mmol/l)

- Chromium picolinate had a significant effect on fasting glucose, -0.8 mmol/l (-1.2 to -0.3 mmol/l). Doses of 400 or 1,000µg/day appear to have had greater effects than lower doses.

- For chromium chloride, there was no significant effect on fasting glucose, -0.3 mmol /l (95% CI, -0.9 to +0.2 mmol /l).

**Lipids:**

- The overall estimate of effect for chromium supplementation was nonsignificant for LDL cholesterol, -0.31mmol/l (95% CI;-0.73 to +0.11 mmol/l).
- Individual studies found no difference in effect between different chromium formulation doses on HDL cholesterol
- Overall estimates for the tested chromium supplements were nonsignificant in participants with type 2 diabetes for Triglycerides

Hence, the above review suggested that chromium supplementation improved glycemia among patients with diabetes.

**Vitamin C, Vitamin E and combination of vitamin C & E**
(Subjects: Type 2 diabetics, type 1 diabetics and pregnant type 1 diabetics)

Hui C et al investigated the effects of high-dose oral vitamin C to alter endothelial dysfunction and insulin resistance in Type 2 diabetes.[27] Thirty-two diabetic subjects with low plasma vitamin C (<40 μM) were subsequently enrolled in a randomized, double-blind, placebo controlled study of vitamin C (800 mg/day for 4 wk). Insulin sensitivity (determined by glucose clamp) and forearm blood flow in response to acetylcholine, sodium nitroprusside (SNP), or insulin (determined by plethysmography) were assessed before and after 4 weeks of treatment. All antidiabetic and antihypertensive medications were stopped for 1 week before subjects were assessed at the beginning and the end of treatment with either vitamin C or placebo. Thus subjects had their medication withdrawn for 1 week before each glucose clamp and forearm blood flow (FBF) study. Results were shown below:

- In the placebo group (n = 17 subjects), plasma vitamin C (22± 3 μM), fasting glucose (159 ± 12 mg/dl), insulin (19 ± 7 μU/ml), did not change significantly after placebo treatment.
- In the vitamin C group (n = 15 subjects), basal plasma vitamin C (23± 2 μM) increased to 48 ± 6 μM after treatment, but this was significantly less than that expected for healthy subjects (>80μM).
- Endothelium-dependent and independent vascular function was assessed by measuring forearm blood flow (FBF) in response to graded intra-arterial infusions of acetylcholine and sodium nitroprusside (SNP), respectively. No significant changes in fasting glucose (156± 11 mg/dl), insulin (14± 2 μU/ml or forearm blood flow in response to acetylcholine, SNP, or insulin were observed after vitamin C treatment.

This study suggested that high-dose oral vitamin C therapy, resulting in incomplete replenishment of vitamin C levels, is ineffective at improving endothelial dysfunction and insulin resistance in Type 2 diabetes.

Gaede P et al did a double blind randomized, cross over trial on thirty Type 2 diabetic patients with urinary albumin excretion rate (AER) 30-300 mg/24 h which were included from the Steno Diabetes Centre, Denmark.28 All patients were treated with oral hypoglycaemic agents or insulin or diet. Patients with BP > 180/ 100 mmHg diuretics calcium antagonist or blockers were given. Patients received vitamin C (1250 mg) and vitamin E (680 IU) per day or matching placebo for 4 weeks with a 3-week wash-out period between treatment periods in random order. The result showed that:

- Combined treatment with vitamin C and E reduced urinary albumin excretion rate (AER) by 19% (95% CI; 6% -34%) (p = 0.04), whereby urinary AER was 197 mg/24 h (95% CI; 114 mg/24 h - 341 mg/24 h) in the treatment group versus 243 mg/24 h (146 mg/24 h - 404 mg/24 h) in the control group.
- No changes were seen in serum creatinine, haemoglobin A1C or blood pressure.
- Fasting plasma concentrations of vitamin C and E increased in all patients during active treatment (mean vitamin C; 79.4 µmol/L (SD 27.8) versus 41.9 µmol/L (SD18.4) in control group and vitamin E 47.0 µmol/L (SD19.8) versus 29.5 µmol/L (SD15.3) in control, P < 0.000001).

Short-term treatment with vitamin C and E in pharmacological doses lowers AER in Type 2 diabetic patients with micro/macroalbuminuria. Further long-term, large-scale studies of this albuminuria reducing treatment modality are warranted.

McCance DR et al did a multicentre randomised placebo controlled trial between April 2003, and June 2008 whereby 762 women with type 1 diabetes preceding pregnancy, presentation between 8 weeks' and 22 weeks' gestation, singleton pregnancy, and age 16 years or older from 25 UK antenatal metabolic clinics were included in the study.[29] Women were randomly allocated in a 1:1 ratio to receive 1000 mg vitamin C and 400 IU vitamin E (a-tocopherol) or matched placebo daily until delivery. The primary endpoint was pre-eclampsia, which we defined as gestational hypertension with proteinuria. Analysis was by modified intention to treat. The results showed that:

- Overall, 127 (17%) women developed pre-eclampsia. Risk of pre-eclampsia did not differ between vitamin and placebo groups
- Rates of pre-eclampsia did not differ between vitamin (15%, n=57) and placebo (19%, 70) groups (risk ratio 0·81, 95% CI 0·59–1·12).
- No adverse maternal outcome including delivery after a hypertension-related admission before 34 or 37 weeks
- There were no significant differences between vitamin and placebo groups for any clinical neonatal outcome including fetal malformation, fetal loss, infant death, or miscarriage.
- Mean birthweights for both vitamin and placebo groups; risk of birthweights of 2500 g or less (RR 0·82, 95% CI 0·56–1·20) and 4000 g or more (1·25, 0·95– 1·64) did not differ between groups.

Hence, supplementation with vitamins C and E did not reduce risk of pre-eclampsia in women with type 1 diabetes.

Lonn E et al evaluated the effects of vitamin E supplementation on major cardiovascular outcomes in people with diabetes.[30] The Heart Outcomes Prevention Evaluation (HOPE) trial is a randomized clinical trial with a 2 by 2 factorial design, which evaluated the effects of vitamin E and of ramipril in patients at high risk for CV events in Canada, U.K., Argentina, and Brazil. Patients were randomly allocated to daily treatment with 400 IU vitamin E and with 10 mg ramipril or their respective placebos and were followed for an average of 4.5 years. There were 3,654 subjects with diabetes. Besides intervention, patients were still on their normal diabetic care. The results were:

- The primary study outcome was the composite of myocardial infarction, stroke, or CV death. There was no significant interaction between the study treatments (ramipril and vitamin E) for the primary, secondary and other study outcomes.
- In the active vitamin E group, 325 /1838 (17.7%) people with diabetes had a primary outcome event that is Composite of myocardial infarction, stroke, or CV death) versus 313 /1816 (17.2%) in the control group (RR =1.03, 95% CI; 0.88–1.21).
- There were no significance differences between the study groups in the rates of myocardial infarction (MI ) events 212/1838 (11.5%) for treatment group versus 209/1816 (11.5%) for the control group.
- There were no significance differences between the study groups in the stroke events; 103 subjects (5.6%) in vitamin E group versus 84 subjects (4.6%)in the control group(RR=1.21, 95% CI; 0.91–1.62).
- There were no significant differences between the study groups on CV death, 142 subjects (7.7%) in vitamin E group versus 145 subjects (8.0%) in control group ( RR = 0.97, 95% CI; 0.77–1.23).
- There were no significant differences between the study groups on total mortality, 218 (11.9%) in vitamin E group versus 232 (12.8%) in control group (RR= 0.93, 95% CI; 0.77–1.12).
- Urinary albumin-to-creatinine ratio was measured in 3,574 (97.8%) participants at baseline, in 3,140 (88.9% of those alive) at 1 year, and in 2,740 (85.9% of those alive) at study end. The albumin-to creatinine ratio did not differ significantly between the two study groups at baseline, at 1 year, or at study end. During followup, 361 (9.9%) study participants developed an albumin-to-creatinine ratio >36 mg/mmol and were asked to provide a 24-h urine collection to test for overt nephropathy. Results were available for 308 (85.3%) patients. In the vitamin E arm, 146 (7.9%) study participants developed overt nephropathy versus 131 (7.2%) study participants in the placebo arm (*P*= 0.37; this analysis uses as a definition of overt nephropathy the presence of significant proteinuria or albuminuria as defined above or albumin to- creatinine ratio>36 mg/mmol.

Hence, the above study suggested that the daily administration of 400 IU vitamin E for an average of 4.5 years to middle-aged and elderly people with diabetes and CV disease and/or additional coronary risk factor(s) has no effect on CV outcomes or nephropathy.

Skyrme-Jones RA et al did a randomized clinical trial that evaluated the effects of vitamin E supplementation (1,000 IU for three months) on endothelial vasodilator function (EVF) and systemic arterial compliance (SAC) in forty one type 1 diabetes mellitus subjects.[31] The authors assessed the endothelial vasodilator function (EVF) in the brachial artery (using noninvasive ultrasound, flow-mediated vasodilation [FMD]) and in the forearm resistance vessels (by flow responses to intrabrachial acetylcholine [ACh]) and measured SAC (simultaneous aortic blood flow and carotid pressure measurements) before and after active or placebo therapy. The results were as follows:

- There was no time-dependent change in FMD or in the response to acetylcholine or systemic arterial compliance (SAC) in the placebo group. A significant improvement in endothelium dependent flow-mediated vasodilation in the brachial artery (FMD) (2.6 ± 0.6% to 7.0 ±6 0.7 %,) were observed in those randomized to vitamin E therapy.
- Systemic arterial compliance was not affected by vitamin E (0.41 ± 0.03 versus. 0.49 ± 0.06 arbitrary compliance units).
- The change in FMD was related to the change in low density Lipoprotein (LDL) vitamin E content VEC, whereby as the LDL vitamin E increases, so does the magnitude of FMD($r = 0.42$, $p \leq 0.05$)
- Reduced oxidative susceptibility after vitamin E supplementation is associated with improved FMD ($r = 0.64$, $p \leq 0.0001$).

This study suggested that short-term daily oral supplementation with vitamin E improves endothelial vasodilator function (EVF) in both the conduit and resistance vessels of young subjects with type I DM.

Milman U et al did a randomized control trial on 1434 DM type 2 individuals ≥55 years of age with the Hp 2-2 genotype at Carmel Medical Center, Israel.[32] The aim was to investigate whether vitamin E could reduce cardiovascular events in DM individuals with the Hp 2-2 genotype. The Haptoglobin (Hp) is a major antioxidant protein and a determinant of cardiovascular events in patients with T2DM. The Hp gene is polymorphic with 2 common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 allelic product. Subjects were randomized to vitamin E (400 U/d) or placebo. The primary composite outcome was myocardial infarction, stroke, and cardiovascular death.

- At the first evaluation of events (first interim analysis), 18 months after initiating the study, the primary outcome, which is the composite outcome of myocardial infarction, stroke, and cardiovascular death was significantly reduced in individuals receiving vitamin E 16 / 726(2.2%) compared with placebo 33/708(4.7%; *P*=0.01) with hazard ratio 0.47(95% CI; 0.27 to 0.82) and led to early termination of the study.

This study suggests that a pharmacogenomic approach may be useful to identify a large subgroup of DM individuals with the Hp 2-2 Genotype who could potentially derive cardiovascular benefit from Vitamin E supplementation.

### L-carnitine

(Subjects: Type 2 diabetic patients)

Sima AAF et al did a multicenter study from 28 U.S. and Canadian centers (U.S.-Canadian Study [UCS]) and 34 U.S., Canadian, and European centers (U.S.-Canadian-European Study [UCES]). The authors did a double-blind, randomized, contolled trial on type 1 and type 2 diabetic patients (1,346 patients) with diabetic polyneuropathy (DPN) according to the San Antonio criteria.[33] Acetyl-L-carnitine (ALC) was given in the treatment group at two doses (500 or 1,000 mg) given three times a day (t.i.d.) for 1 year. The results were as follows:

- Morphometric parameters included total myelinated fiber number, mean fiber size, fiber density, fiber occupancy, and axon-to myelin ratio. These measurements were combined in an O'Brien's average rank score. Data showed significant improvements in sural nerve fiber numbers and regenerating nerve fiber clusters. Morphometric evaluations of sural nerve biopsies revealed a significant increase in the O'Brien rank score for all biopsy parameters in the 500-mg ALC arm (144.1 ± 28.9 vs. 132.6 ± 37.8, *P*=0.027), with a significant increase in fiber numbers (-14 ± 197 versus -98± 352; *P*= 0.049) and a significant increase in regenerating clusters (-3.3 ± 8.0 versus -27.9±9.1; *P*=0.033).

- Pain as the most bothersome symptom showed significant improvement in patients taking 1,000 mg ALC. From *Pain visual analogue scale; the results were* -22.89 ± 28.57 for the ALC 1000 mg group versus -15.11 ± 27.89 in placebo after week 26 and -23.82 ± 31.45 in ALC group versus -12.40 ± 29.11 in placebo group at week 52.

- Vibration perception improved significantly in the fingers in both the 500- and 1,000-mg ALC t.i.d. groups (*P*= 0.040 and *P* =0.010) and in the toes in the 1,000-mg t.i.d. group (*P* = 0.047).

This study suggests that ALC treatment is efficacious in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy.

Malaguarnera M et al did a randomized control trial to evaluate the efficacy of L-carnitine on the reduction of oxidized LDL cholesterol in patients with T2DM.[34] Eighty-one patients with diabetes from Cannizzaro Hospital, Catania, Italy) were divided into two groups. Group 1 received 2 gm/day L-carnitine, which was divided into 2 equal doses of one 1-gm tablet after breakfast and one 1-gm tablet after dinner for 3 months. Group 2 received a placebo according to the same regimen and for the same duration. At the end of the study period, the L-carnitine-treated patients showed significant improvements compared with the placebo group in the following markers:

- Oxidized LDL levels decreased by 15.1 U/L in L-carnitine group compared with 3.0 U/L in placebo group (P< 0.001);

- LDL cholesterol decreased by 0.45 mmol/L in L-carnitine group compared with 0.16 mmol/L in placebo group (P < 0.05); triglycerides decreased by 1.02 mmol/L compared with 0.09 mmol/L in placebo group (P<, 0.001);

- Apolipoprotein A1 concentrations decreased by 0.12 mg/ dL in L-carnitine group compared with 0.03 mg/ dL in placebo group (P<0.05); apolipoprotein B-100 concentrations decreased by 0.13 mg/ dL in L-carnitine group compared with 0.04 mg/dL in placebo group (P <0.05);

- Thiobarbituric acid– reactive substance concentrations decreased by 1.92 nmol/ mL in L-carnitine group compared with 0.05 nmol/mL in placebo group (P<0.001), and conjugated diene concentrations decreased by 0.72 µmol/mL in L-carnitine group compared with 0.110.72 µmol/mL in the placebo group (P , 0.001).

- No significant decrease was observed in the fasting plasma glucose concentrations in either the L-carnitine- or placebo treated groups compared with baseline. In the L-carnitine-treated group, however, there was a significant decrease in Hb A1C of 0.6% (P < 0.001) after 12 week treatment.

This study suggests that oral administration of L-carnitine reduces oxidized LDL cholesterol levels in patients with type 2 diabetes.

### Alpha lipoic Acid

(Subjects: Type 2 diabetic patients)

Mijnhout GS et al did a systematic review of the literature to evaluate the effects of alpha lipoic acid on symptomatic peripheral neuropathy in patients with diabetes mellitus.[35] For study selection, the following inclusion criteria were used: (1) RCTs on alpha lipoic acid, (2) a study population consisting of patients with DM and peripheral neuropathic pain, and (3) use of the total symptom score (TSS) as the outcome measure. Five RCTs and one meta-analysis were found. The dosage of alpha lipoic acid ranged from 100 to 1800 mg per day. Intravenous alpha lipoic acid was given for three weeks, and oral administration varied between three weeks and six months. The primary outcome measure in this meta-analysis was the total symptom score (TSS). The TSS is a questionnaire in which the patient is asked to assess the intensity (absent, mild, moderate, severe) and the frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness) resulting in a scaled score in which 0 means no symptoms and 14.64 means that all four symptoms are severe and more or less continuously present. A 30% change on this scale is considered to be clinically relevant (or ≥2 points in patients with a starting score ≤4 points).

- In these studies an average 50% reduction was seen in the TSS with the oral or intravenous administration of at least 600 mg per day. However, when compared to the subjects in the control groups, the reduction in TSS was actually less than the clinically relevant threshold of 30%, as the TSS in the control group also decreased. This was particularly evident in the studies where alpha lipoic acid was administered orally.

- Overall, the pooled standardized mean difference estimated from all trials revealed a reduction in TSS scores of −2.26 (CI: −3.12 to −1.41; *P* =0.00001) in favour of alpha lipoic acid administration. Subgroup analyses of oral administration showed a mean difference of −1.78 (CI: −2.45 to −1.10; *P* = 0.00001) and intravenous administration showed a mean difference of −2.81 (CI: −4.16 to −1.46; *P* = 0.0001). Hence, when given intravenously at a dosage of 600 mg/day over a period of 3 weeks, alpha lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain.

Caution should be taken when giving alpha lipoic acid as out of all reported adverse events, only heart rate and rhythm disorders were observed significantly more frequently in patients treated with alpha lipoic acid compared to patient treated with placebo (6.9% versus 2.7%, *P* 0.047).

### Cinnamon

(Subjects: Type 1 diabetics, type 2 diabetics and pre-diabetics)

Cinnamon, obtained from the inner bark of plants *cinnamomum*, has been used as a spice in cookery worldwide and is an important ingredient in the traditional Chinese medicine and Ayurveda for centuries. The dry bark of cinnamon trees is rich in botanical source of polyphenolics and has been used to improve general health.

Ziegenfuss TN et al did a randomized controlled study to determine the effects of supplementation with a water-soluble cinnamon extract (Cinnulin PF®) on body composition and features of the metabolic syndrome.[36] Twenty-two subjects with prediabetes and the metabolic syndrome (mean ± SD: age, BMI, systolic blood pressure [SBP], fasting blood glucose [FBG]: mean age; 46.0 ± 9.7 y; 33.2 ± 9.3 kg/m$^2$; 133 ± 17 mm Hg; 114.3 ± 11.6 mg/dL) were recruited from northeastern Ohio and were randomly assigned to supplement their diet with either Cinnulin PF® (500 mg/d) or a placebo for 12-weeks.

- Subjects in the Cinnulin PF® group had significant decreases in FBG (-8.4%: 116.3 ± 12.8 mg/dL [pre] to 106.5 ± 20.1 mg/dL [post], p<0.01),
- SBP (-3.8%: 133 ± 14 mm Hg [pre] to 128 ± 18 mm Hg [post], p<0.001),
- and increases in lean mass (+1.1%: 53.7 ± 11.8 kg [pre] to 54.3 ± 11.8 kg [post], p<0.002) compared with the placebo group.
- Additionally, within-group analyses uncovered small, but statistically significant decreases in body fat (-0.7%: 37.9 ± 9.2 % [pre] to 37.2 ± 8.9 % [post], p<0.02) in the Cinnulin PF® group.
- No significant changes in clinical blood chemistries were observed between groups over time.

These results showed that cinnamon supplementation may reduce FBG and SBP, and improving body composition in men and women with the metabolic syndrome and suggest that this spice can reduce risk factors associated with diabetes and cardiovascular diseases.

Lu T et al did a randomized control trial to investigate whether cinnamon supplements were able to aid in treatment of type 2 diabetes by improving blood glucose control.[37] A total of 66 Chinese patients with type 2 diabetes were recruited. All subjects were outpatients from Xuhui Central Hospital, Shanghai. Sixty-nine patients (including 44 women and 25 men with age >48 years) with type 2 diabetes and who had levels of HbA1c greater than 7.0% and FBG greater than 8.0 mmol/L were randomly divided into 3 groups: placebo, low dose and high-dose groups. The low- and high-dose groups took either 2 or 6 cinnamon tablets, respectively; with each tablet containing 60 mg of cinnamon extract for 3 months (all subjects took the same kind of prescribed antidiabetic medication). The results showed that:

- The levels of HbA1c and FBG were not significantly altered in the placebo group with HbA1c changing from 8.92% to 8.93% and FBG from 8.92 to 8.71 mmol/L and no significant differences between pre- and post treatment. However, both the HbA1c and FBG levels were significantly reduced in post treatment in the low- and high-dose groups. The HbA1c level was decreased from 8.90% ± 1.24 to 8.23% ± 0.99 with a reduction of −0.67% (95% CI; −1.09% to −0.25%) in the low dose group and from 8.92% ± 1.35 to 8.00% ± 1.00 in the high-dose group with an average reduction of −0.93% (95% CI; −1.38% to −0.47%).

- FBG levels were significantly reduced in patients in the low-dose from 9.00 mmol/L ± 1.23 to 7.99 mmol/L ± 1.05 with a reduction of −1.02 mmol/L (−1.61 mmol/L to −0.42 mmol/L) and high-dose groups from 11.21mmol/L ± 2.21 to 9.59 mmol/L ± 1.66 with a reduction of −1.62 mmol/L (95% CI; −2.32 mmol/L to −0.93 mmol/L) , whereas they were not changed in the placebo group from 8.92 mmol/L ± 1.21 to 8.71 mmol/L ± 2.01 with a small reduction of −0.22 mmol/L (95% CI;−1.34 mmol/L to 0.91 mmol/L).

- The blood triglyceride levels were also significantly reduced in the low-dose group from 2.93 mmol/L ± 2.08 to 2.15 mmol/L ± 1.19 with a reduction of −0.78 mmol/L (95% CI;−1.32 mmol/L to −0.23 mmol/L).

- The blood levels of total cholesterol, highdensity lipoprotein cholesterol, low-density lipoprotein cholesterol, and liver transaminase remained unchanged in the 3 groups.

This study indicates that cinnamon supplementation was able to significantly improve blood glucose control in Chinese patients with type 2 diabetes.

Leach MJ and Kumar S did a systematic review whereby ten prospective, parallel-group design, randomised controlled trials, involving a total of 577 participants with type 1 and type 2 diabetes mellitus, were identified.[38] In the trials included Oral monopreparations of cinnamon (predominantly Cinnamomum cassia) were administered at a mean dose of 2 g daily, for a period ranging from 4 to 16 weeks and compared to placebo. The results showed:

- The effect of cinnamon on fasting blood glucose level was inconclusive. Eight trials reported data on fasting blood glucose levels for 338 patients. There was no statistically significant difference in FBG level between cinnamon and placebo (mean difference -0.83 mmol/L (95% CI; -1.67 mmol/L to 0.02 mmol/L, P=0.06) 2 trials with 98 patients reported a mean difference of -0.08mmol/L (95% CI; 0.39 mmol/L to 0.22 mmol/L, P=0.59).
- No statistically significant difference in HbA1c whereby six trials reported a difference of -0.06% ( 95% CI; -0.29 % to 0.18%, P=0.63.)
- There was no statistically significant difference on serum insulin whereby 2 trials stated that the mean difference on serum insulin between cinnamon and placebo group was -6.77pmol/L (95% CI; -37.0 pmol/L to 23.46 pmol/L, p=0.66).
- There were insufficient data to pool results for insulin sensitivity.
- No trials reported health-related quality of life, morbidity, mortality or costs. Adverse reactions to oral cinnamon were infrequent and generally mild in nature.

The authors stated that there is insufficient evidence to support the use of cinnamon for type 1 or type 2 diabetes mellitus. Further trials, which address the issues of allocation concealment and blinding are now required.

### Fenugreek

(Subjects: Type 2 diabetes patients)

Fenugreek, also known by its scientific name of *trigonella foenum-graecum L., leguminosae*, belongs to the plant family *fabaceae* (or *leguminosae*). It grows in most of the countries around world with major production in Asia, Europe and North American including United States.

Mitra A and Bhattacharya D did a single blind trial on 80 randomly selected newly diagnosed type-2 diabetes patients.[39] Patients were initially divided in 5 groups of 16 each. Group 1 received 25 g, Group 2 received 50 g, Group 3 received 75 g and group 4 received 100 g of fenugreek seeds for 2 months along with 2.5 g of *Tulsi* leaves powder, while Group 5 acted as control for 2 months with normal diet. The results showed that:

- With 25 g/day of Fenugreek total cholesterol (TLC) was reduced from initial value of 229 ± 12 mg/dl to 227 ± 10 mg/dl while the effects of 50 g/day of fenugreek was a reduction from initial value of 233 ± 10 mg/dl to 232 ± 7 mg/dl. These reductions of TLC values were statistically insignificant. With 75 g/day of Fenugreek the TLC values were reduced from 230 ± 7 mg/dl to 224 ± 9 mg/dl, a reduction of 2.88% ($P \leq 0.05$). 100 g/day of Fenugreek caused a decrease of TLC values from 232 ± 9 mg/dl to 219 ± 7 mg/dl, a reduction of 6.18% ($P \leq 0.05$).

- High density Lipoprotein cholesterol (HDLC) values showed that with 25 g/day of Fenugreek, the initial value of 35 ± 4 mg/dl was increased to 38 ± 3 mg/dl, an increase of 8.62% ($P \leq 0.075$). 50 g/day of Fenugreek caused increase of HDLC values from 36 ± 3 mg/dl was increased to 40 ± 5 mg/dl, an increase of 11.12% ($P \leq 0.05$). With 75 g/day of fenugreek dose, HDLC values were increased from 38 ± 5 mg/dl was increased to 44 ± 3 mg/dl, an increase of 15.15% ($P \leq 0.025$). 100 g/day of fenugreek dose caused increase of HDLC values from 34 ± 3 mg/dl to 42 ± 5 mg/dl, an increase of 23.53% ($P \leq 0.25$).

- Low doses of fenugreek (25-50g/day) did not show any statistical significant change on LDLC. However, 75g/day of Fenugreek caused a decrease of LDLC values from 156 ± 5 mg/dl to 147 ± 5 mg/dl, a reduction of 5.82% ($P \leq 0.075$). With 100 g/day of Fenugreek LDLC values was reduced from 160 ± 5 mg/dl to 147 ± 9 mg/dl, a reduction of 8.15% ($P \leq 0.05$).

- Analyzing triglycerides (TG), 25 g/day of Fenugreek caused reduction of TG values from 180 ± 12 mg/dl to 175 ± 8 mg/dl, the reduction was 2.75% ($P \leq 0.05$). With 50 g/day of Fenugreek TG values was reduced from 185 ± 12 mg/dl to 174 ± 5 mg/dl, the reduction was 5.94% ($P \leq 0.05$). 75 g/day of Fenugreek caused a decrease of TG values from 180 ± 5 mg/dl to 166 ± 6 mg/dl, a reduction of 7.34% ($P \leq 0.025$). With 100 g/day of Fenugreek TG values was reduced from 185 ± 9 mg/dl to 160 ± 12 mg/dl, a reduction of 13.14% ($P \leq 0.025$).

- FBG values showed that with 25 g/day of Fenugreek, the initial value of 184 ± 11 mg/dl was reduced to 176 ± 7 mg/dl, a decrease of 4.08% ($P \leq 0.025$). With 50 g/day of Fenugreek FBG values was reduced from 184 ± 7 mg/dl to 170 ± 7 mg/dl, the reduction was 7.84% ($P \leq 0.05$). 75 g/day of Fenugreek caused a decrease of FBG values from 183 ± 7 mg/dl to 164 ± 5 mg/dl, a reduction of 10.38% ($P \leq 0.05$). With 100 g/day of Fenugreek FBG values was reduced from 185 ± 10 mg/dl to 165 ± 7 mg/dl, a reduction of 10.56% ($P \leq 0.05$).

The present study shows that fenugreek seeds decrease blood glucose and triglyceride levels and have significant effect on LDL or HDL cholesterol when consumed at higher doses.

### Thiamine

(Subjects: Type 2 diabetes patients)

Rabbani N et al did a randomized controlled study to assess whether oral supplements of thiamine could reverse microalbuminuria in patients with type 2 diabetes.[40] Type 2 diabetic patients (21 male, 19 female) with microalbuminuria were recruited at the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan. All patients received usual diabetic care (insulin, diet or hypoglycaemic agents (sulfonylureas, metformin and thiazolidinediones). Patients were given 3×100 mg capsules of thiamine or placebo per day for 3 months with a 2 month follow-up washout period.

- The primary endpoint of this study was effect on urinary albumin excretion (UAE). After the treatment period, patients receiving thiamine therapy had decreased median UAE, with respect to patients receiving the placebo (30.1 mg/24 h in thiamine group versus 35.5 mg/24 h in placebo; p<0.01). UAE was decreased significantly with respect to baseline in the patients treated for 3 months with thiamine (−17.7 mg/24 h;p<0.001) but not in patients treated with placebo.
- Linear regression of UAE in relation to treatment time indicated that the rate of decrease in UAE was increased about fourfold in patients treated with thiamine with respect to placebo (5.62 versus 1.52 mg/24 h)
- After therapy for 3 months, regression of microalbuminuria to normal urinary albumin had occurred in 35% of the patients.
- There was no significant effect of thiamine supplementation on glycaemic control, dyslipidaemia, BP, GFR or markers of vascular dysfunction during the treatment period.

In this pilot study, to complement standard diabetic care, high-dose thiamine therapy, produced a regression of UAE in type 2 diabetic patients with microalbuminuria. Thiamine supplements at high dose may provide improved therapy for early-stage diabetic nephropathy

## SAFETY

### Vitamin E

(Subjects: Type 2 diabetes patients)

Ward NC, Wu JH did a randomized in a double-blind, placebo-controlled trial to investigate the effect of alpha-tocopherol and gamma-tocopherol supplementation on 24-h ambulatory BP) and heart rate, vascular function and oxidative stress in fifty –eight individuals with type 2 diabetes from Perth, Australia.[41] Participants were randomized to a daily dose of 500 mg/day RRR-alpha-tocopherol, 500 mg/day mixed tocopherols (60% gamma-tocopherol) or placebo for 6 weeks. All patients still continue with their prescribed diabetic medication. The results showed that:

- Treatment with alpha-tocopherol significantly increased systolic BP (SBP) [7.0 (5.2, 8.8) mmHg, P < 0.0001], diastolic BP (DBP) [5.3 (4.0, 6.5) mmHg, P < 0.0001], pulse pressure [1.8 (0.6, 3.0) mmHg, P < 0.005] and heart rate [2.0 (0.6, 3.3) bpm, P < 0.005] versus placebo.
- Treatment with mixed tocopherols significantly increased systolic BP [6.8 (4.9, 8.6) mmHg, P < 0.0001], diastolic BP [3.6 (2.3, 4.9) mmHg, P < 0.0001], pulse pressure [3.2 (2.0, 4.4) mmHg, P < 0.0001] and heart rate [1.8 (0.5, 3.2) bpm, P < 0.01] versus placebo.
- Treatment with alpha-tocopherol or mixed tocopherols significantly reduced plasma F2-isoprostanes versus placebo, but had no effect on urinary F2-isoprostanes.
- Endothelium-dependent and independent vasodilation was not affected by either treatment.

Treatment with either alpha- or mixed tocopherols significantly increased BP, pulse pressure and heart rate in individuals with type 2 diabetes.

### Vitamin B6, B12 and folic acid combination

(Subjects: Type 1 and type 2 diabetes patients)

Hyperhomocysteinemia is frequently observed in patients with diabetic nephropathy vitamin B therapy (folic acid, vitamin B6, and vitamin B12) has been shown to lower the plasma concentration of homocysteine. House AA et al did a randomized control trial to determine whether vitamin B therapy can slow progression of diabetic nephropathy and prevent vascular complications.[42] A multicenter, randomized, controlled trial at 5 university medical centers in Canada was conducted between May 2001 and July 2007. In the study, 238 participants who had type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy were included. Participants were randomized 1:1 to receive a single tablet of B vitamins that contained 2.5mg/d of folic acid, 25mg/day of vitamin B6, and1mg/d of vitaminB12, or a matching placebo. All patients still continue with their prescribed medication. The mean (SD) follow-up during the trial was 31.9 (14.4) months. The results showed that:

- The mean (SD) baseline GFR was 54.7 (29.5) mL/min/1.73 $m^2$. At 36 months, radionuclide glomerular filtration rate (GFR) decreased by a mean (SE) of 16.5 (1.7) mL/min/1.73 $m^2$ in the B-vitamin group compared with 10.7 (1.7) mL/min/1.73 $m^2$ in the placebo group (mean difference −5.8; 95% CI, −10.6 to −1.1 *P*=.02).
- There was no difference in requirement of dialysis (hazard ratio [HR], 1.1; 95% CI, 0.4-2.6; *P*=.88).
- The 36-month risk of a composite outcome, including MI, stroke, revascularization, and all-cause mortality, in the B-vitamin group occurred more often, which was about double that in the placebo group (HR, 2.0; 95% CI, 1.0-4.0; *P*=.04). The 36-month risks of the composite end point was 23.5% (95% CI, 15.0%-32.0%) in the B-vitamin group and 14.4% (95% CI, 6.9%- 21.8%) in the placebo group.
- The baseline mean plasma total homocysteine was 15.5 (5.2) µmol/L. Plasma total homocysteine decreased by a mean (SE) of - 2.2 (0.4) µmol/L at 36 months in the B-vitamin group compared with a mean (SE) increase of 2.6 (0.4) µmol/L in the placebo group resulting in a significant mean difference of −4.8 (95% CI, −6.1 to −3.7; *P*< *0*.001, in favor of B vitamins).

In this randomized trial of participants with diabetic nephropathy and stages 1 to 3 chronic kidney disease, the use of high doses of B vitamins (containing 2.5 mg/d of folic acid, 25 mg/d of vitamin B6, and1mg/d of vitamin B12) compared with placebo resulted in a greater decrease in GFR and an increase in MI and stroke and suggesting harm to these patients. It would be prudent to discourage the use of high-dose B vitamins as a homocysteine- lowering strategy outside the framework of properly conducted clinical research. Hence, it is advisable to be cautious when prescribing high doses of vitamin B complex to patients with diabetes.

## COST/ COST EFFECTIVENESS

There was no retrievable scientific evidence on the cost/ cost-effectiveness of nutraceuticals to complement therapy for diabetes.

## DISCUSSION

According to Deng R in his narrative review there were four patent applications that described usages and applications of fenugreek in managing metabolic diseases including hyperglycemia and diabetes.[43] Clinical studies with human volunteers as well as other small trials showed a dosage form of 500 mg given once or twice daily either alone or in combination with standard, synthetic anti-diabetic drugs such as metformin and glipizide provided beneficial effects on controlling plasma glucose levels. However, such hypoglycemic effect is not certain or diminished in healthy, obese or overweight subjects.[43-44] Additional trials with high quality study design and increased sample size are required to substantiate the claim of fenugreek's hypoglycemic effect.

A large number of preclinical studies support the claim that momordica charantia is able to lower plasma glucose levels. However, the results from human clinical trials are not conclusive.[43,45,46] The results from three early clinical trials support the hypoglycaemic activity of momordica charantia. Drinking of the aqueous homogenized suspension of the vegetable pulp resulted in a significant reduction in FBG and postprandial sugar levels. However, such claim was challenged by the results from two randomized and placebo-controlled trials. Supplementation with momordica charantia extract did not significantly reduced FBG and HbA1c levels although the HbA1c levels were decreased in treatment group compared with the control group. From our review, bitter melon for type 2 diabetics had no significant change in blood sugars levels and also no statistically significant difference in the glycaemic control compared to placebo.[24-25] Additional clinical studies with improved experimental design, standardized preparation and dose, and increased size are required to firmly establish the hypoglycemic activity of momordica charantia.

Some studies showed a significant reduction in FBG levels that were detected compared to the baseline in the cinnamon group.[43, 44, 47-52] However, the changes were not significant when compared to placebo group. No significant differences between the cinnamon and placebo groups in FBG, HbA1c and insulin levels were detected at the end of the trial. The authors concluded that cinnamon supplement did not have hypoglycemic effects in type 2 diabetic patients and the effects of cinnamon might differ by population. [43, 44, 47-52] Such hypoglycemic effect was not detected in specific subject populations such as type 1 diabetic patients and postmenopausal type 2 diabetic patients. [43, 44, 47-52] Therefore, additional clinical studies with more defined subject populations are warranted.

In an article by American Diabetes Association it was mentioned that the FDA concluded that although a small study suggested that chromium picolinate may reduce insulin resistance, the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes was uncertain.[53-54] Therefore larger high quality randomised clinical trials are warranted to provide solid scientific evidence on the long term safety and effectiveness of chromium for diabetics.

At the moment there is insufficient evidence to demonstrate efficacy of individual nutraceuticals and supplements in diabetes management. The various nutraceuticals should standardize the content of active ingredients. Further high quality randomised clinical trials are needed before any nutraceutical can be used as an adjunct to diet or medications for diabetes patients who cannot achieve target of glycemic control.

## CONCLUSION

### Efficacy/effectiveness of nutraceutical therapy as a complement for diabetes treatment

**Fish oil (EPA & DHA)**

- There was good level of evidence to suggest that Fish oil (EPA & DHA) for type 2 diabetics **did not** result in any statistically or clinically significant effect for fasting glucose, HbA1c, total cholesterol, or HDL cholesterol. One RCT on thirty four subjects showed that six weeks supplementation with EPA & DHA improved postprandial macrovascular and microvascular function suggesting a protective vascular effect of EPA & DHA. However, further long-term, large-scale studies are warranted to establish this effect.

**Bitter melon**

- There was fair to good level of evidence to show that bitter melon for type 2 diabetics had **no significant change** in blood sugars levels and also no statistically significant difference in the glycaemic control compared to placebo.

**Chromium supplementation**

- There was good level of evidence to suggest that for type 2 diabetic patients, chromium supplementation (brewer's yeast 1.28–400 µg/day or Chromium picolinate 60–1,000 µg/day) improved glycosylated hemoglobin levels and fasting glucose but not lipids. However, future studies are needed before definitive claims can be made about the effect of chromium supplementation.

**Vitamin C**

- There was fair to good level of evidence to suggest that high-dose oral vitamin C therapy is **ineffective** at improving endothelial dysfunction and insulin resistance in Type 2 diabetes.

**Vitamin C and E**

- It was found that combined treatment with vitamin C and E in pharmacological doses lowers the albumin excretion rate (AER) in Type 2 diabetic patients with micro/ macroalbuminuria. Further long-term, large-scale studies are warranted to provide evidence of effectiveness on using such treatment modality.

- For **type 1 pregnant diabetes patients**, combined supplementation with vitamin C and E showed **no statistically differences** between vitamin and placebo groups in the rates of pre-eclampsia, for any clinical neonatal outcome including fetal malformation, fetal loss, infant death, or miscarriage.

**Vitamin E**

- There is good level of evidence that 400 IU vitamin E only benefit in subgroup but not all diabetes patients such as DM type 2 with HP 2-2 genotype, where supplementation results in reduction of MI, stroke and CVS mortality.

- In one RCT, short term daily oral supplementation in 41 young type-1 diabetes, with vitamin E (1,000 IU for three months) improves endothelial vasodilator function (EVF) in both the conduit and resistance of the vessels.

**Acetyl-L-Carnitine**

- There was good level of evidence to suggest that 500mg and 1,000mg of acetyl-L-carnitine was found to be **efficacious** in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with diabetic neuropathy. Future trials are needed to establish such beneficial effects.

**Alpha lipoic acid**

- It was found that supplementation with the oral or intravenous administration of at least 600 mg per day with alpha lipoic acid to diabetic patients resulted in a reduction in the Total Symptom Score (TSS) for pain, burning, paresthesia and numbness but when compared to controls, the reduction in TSS was actually less than the clinically relevant threshold of 30%. Also heart rate and rhythm disorders were observed significantly more frequently in patients treated with alpha lipoic acid compared to patient treated with placebo.

**Cinnamon**

- The results of trials on cinnamon were in conclusive as some showed beneficial effects but others don't. Further trials are needed to establish the beneficial effect of this nutraceutical.

**Fenugreek**

- There was fair level of evidence to suggest that fenugreek 25gm to 100gm/day given to newly diagnosed type 2 diabetes patients may be able to reduce FBG levels and cholesterol level in these patients. However a more robust prospective study is warranted to establish this effect.

**Thiamine**

- In a pilot study on type 2 diabetic patients with microalbuminuria, supplementation with high-dose thiamine (300mg.) produced a regression of urinary albumin excretion (UAE) suggesting that thiamine supplements at high dose may provide improved therapy for early-stage diabetic nephropathy. However, more trials are needed to establish this effect.

### Safety profile of using nutraceutical therapy as a complement to the treatment of diabetes

- There was good level of evidence to suggest that supplementation with B vitamins containing folic acid (2.5 mg/d), vitamin B6 (25 mg/d), and vitamin B12 (1 mg/d) to T1DM and T2DM patients with diabetic nephropathy and stages 1 to 3 chronic kidney disease, resulted in a greater decrease events in GFR and also increase events in MI and stroke. Therefore, caution should be taken when giving high doses of vitamin B to diabetic patients.

## RECOMMENDATION

### Nutraceutical therapy as a complement for diabetes

**Based on the above review:**

- Complementary treatment with fish oil, bitter melon and vitamin C, Combination of Vitamin C & E and high doses of B vitamins appeared to offer no benefit in terms of glycaemic control as reflected in HbA1c level, postprandial blood glucose and fasting blood glucose as reported in some studies.
- The effect of cinnamon on fasting blood glucose level and HbA1c was inconclusive.
- The use of high doses of B vitamins (containing 2.5 mg/d of folic acid, 25 mg/d of vitamin B6, and1mg/d of vitamin B12) on participants with diabetic nephropathy and stages 1 to 3 chronic kidney disease resulted in a greater decrease in GFR and an increase in MI and stroke and suggesting harm to these patients.
- Vitamin E supplementation was inconclusive to reduce the composite outcome of myocardial infarction, stroke, and cardiovascular death. A large subgroup of DM individuals with the Hp 2-2 Genotype may potentially derive cardiovascular benefit from Vitamin E supplementation.

Hence, these nutraceuticals (fish oil, bitter melon, high dose vitamin C, and combination of vitamin C & E, high doses of vitamin B6, B12, cinnamon and Vit E) cannot be recommended as a complement therapy for diabetes until futher scientific evidence is obtained to establish their effectiveness and safety.

**Based on the above review:**

- Fenugreek, chromium supplementation (brewer's yeast and chromium picolinate) appears to have significant effects on fasting glucose.
- High dose thiamine seems to lower albumin excretion rates in Type 2 diabetic patients with micro/macroalbuminuria.

- Acetyl-L-carnitine may have potential in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy. It also reduces oxidized LDL cholesterol levels in patients with type 2 diabetes.

- Alpha lipoic acid 600 mg per day supplementation may have potential in alleviating symptoms, particularly pain. However, it should be used with caution as adverse events such as heart rate and rhythm disorders weret observed.

Therefore, more research with larger, high quality randomised clinical trials are warranted to provide more scientific evidence on the long term safety and effectiveness of nutraceuticals such as fenugreek, chromium, Vitamin E, thiamine, Acetyl-L-carnitine and Alpha lipoic acid before these can be recommended as a complementary therapy for diabetes in Malaysia.

Commercially available nutraceutical products are not standardized and vary in the content of active ingredients. Issues such as bioavailability, bioactivity of metabolites, dose/response and toxicity of bioactive compounds need to be considered when presented as nutraceuticals. Interaction of these nutraceuticals with other drugs or between different nutraceuticals when taken as a cocktail of supplements are areas of concern and more research are needed to provide solid evidence on these issues. Sufficient legislative safeguards are essential on the use of nutraceuticals in Malaysia. Until further evidence is available, health professionals should be alerted to the possibility of adverse effects of nutraceuticals, the potential for harmful interactions with other medications and nutritional imbalances due to overuse. In order to have scientific knowledge about the nutraceuticals, public should be educated, where recommended daily doses of these nutraceuticals should be known by each consumer. Hence, several large, well designed, randomized, placebo-controlled studies, powered to detect differences in clinical events, are needed to examine any potential role of nutraceutical therapy as an adjunct to existing treatment paradigms.

# CHAPTER 6: NUTRITIONAL THERAPY AS A COMPLEMENT FOR HYPERTENSION

## INTRODUCTION

Hypertension is a major healthcare problem afflicting nearly 50 million individuals in the United States.[55] Despite its strong causal association with cardiovascular disease complications including myocardial infarction, heart failure, and stroke, the majority of patients with hypertension do not achieve optimal blood pressure control. The prevalence of hypertension is expected to increase with the aging population, growing obesity epidemic, and rising incidence of metabolic syndrome.[56] In Malaysia, the prevalence of hypertension is also rising as demonstrated in the National Health and Morbidity Survey 2011 whereby the prevalence of hypertension among adult of 18 years and above was 32.7%.[2] There was an increasing trend in prevalence with age from 8.1% for hypertension in the 18-19 years old age group reaching a peak of 74.1% among 65-69 year olds.[2]

Nutraceuticals and functional foods have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects".[12] There is, thus, a proliferation of these value-added products aimed at not only keeping one self healthy but also prevention/treatment of various ailments ranging from heart diseases to cancer.[12] Nutraceuticals have been claimed to have a physiological benefit or provide protection against the following diseases: cardiovascular agents, antiobese agents, antidiabetics, anticancer agents, immune boosters, chronic inflammatory disorders, degenerative diseases, hypertension and others. Hence, the purpose of this review is to discuss these issues and provide evidence on the use of nutraceuticals to complement the treatment of hypertension.

## CHARACTERISTICS OF INCLUDED STUDIES

### Study design

Seven studies were included in this review, where five of the studies were systematic reviews with / without meta-analysis and two RCT's. As for the RCT's two of the studies were on safety.

### Participants

Most of the studies participants included patients with hypertension. There were two studies on patients who were having gestational hypertension and no study on pre-hypertensive patients.

### Intervention

Most of the studies were using nutraceuticals with usual care for the intervention group. The nutraceuticals included in the studies using nutraceuticals for hypertension were L. arginine, fish oil, tocopherol (vitamin E) and magnesium.

### Comparators

The comparators were usually patients on usual care with their usual medication, diet or lifestyles.

## Outcome measures

The outcome measures assessed in the studies included: Efficacy/ Effectiveness of nutraceuticals to reduce hypertension, pre-hypertension and gestational hypertension through all cause mortality and cardiovascular effects, reduction in systolic pressure, diastolic pressure, surrogate outcomes or biomarkers, weighted mean differences, adjusted odd ratios (ORs) and relative risks with 95% confidence intervals (CIs) from individual studies, multivariable adjusted hazard ratios with 95% confidence intervals (CIs) from individual studies, adverse events or safety.

### EFFICACY/ EFFECTIVENESS

#### L Arginine

(Subjects: Hypertensive patients)

Dong JY did a systematic review whereby 11 randomized, double-blind, placebo-controlled trials involving 387 participants were included with oral L-arginine intervention ranging from 4 to 24 g/d as the intervention versus placebo.[57] The results of the study showed:

- Compared with placebo, L-arginine intervention significantly lowered systolic BP by 5.39 mm Hg (95% CI −8.54 to −2.25, $P$ = .001) and diastolic BP by - 2.66 mm Hg (95% CI −3.77 to −1.54, $P$ < .001).
- Sensitivity analyses restricted to trials with duration of 4 weeks or longer and to trials in which participants did not use antihypertensive medications yielded similar results.
    - After excluding two trials that showed large systolic BP reductions in response to L-arginine intervention, there was no heterogeneity ($P$ = 0.59, $I^2$ = 0%), and the combined effect size was −3.34 mm Hg (95% CI; −4.93 to −1.86, $P$ < .001).
    - Restricting analysis to 8 trials with duration of 4 weeks or longer did not change the overall BP estimates (systolic BP −3.96 mm Hg, 95% CI, −5.68 to −2.24; diastolic BP -2.62 mm Hg, 95% CI, −4.11 to −1.14).
    - Restricting analysis to 7 trials in which participants did not use antihypertensive medications yielded similar results (systolic BP −3.92 mm Hg, 95% CI, −6.47 to −1.37; diastolic BP −2.50 mm Hg, 95% CI, −3.75 to −1.25).
    - Additional analyses examining the influence of an individual trial on the combined effect size by omitting one trial in each turn yielded a range from −3.66 (95% CI, −5.54 to −1.78) to −5.92 mm Hg (95% CI, −9.33 to −2.51) for systolic BP and a range from −2.40 (95% CI, −3.55 to −1.26) to −3.20 mm Hg (95% CI, −4.68 to −1.73) for diastolic BP.

This meta-analysis provides further evidence that oral L-arginine supplementation significantly lowers both systolic and diastolic BP.

## Calcium

(Subjects: Hypertensive patients, pregnant Hypertensive patients)

Mierlo LAJV et al did a systematic review and a meta-analysis of randomized controlled trials to determine the effect of calcium supplementation on blood pressure (BP).[58] A systematic search for randomized trials of calcium supplementation and BP in non-pregnant subjects was performed in Medline from 1966 to June 2003. Seventy-one trials were identified, 40 of which met the criteria for meta-analysis (total of 2492 subjects). The intervention was daily calcium dose from 355 to 2000 mg (mean: 1200 mg, median: 1055 mg) and the duration of intervention ranged from 3 to 208 weeks (median: 9.5 weeks). The result showed that:

- Calcium supplementation (mean daily dose: 1200 mg) reduced systolic BP by -1.86mmHg (95% confidence interval: -2.91 to -0.81) and diastolic BP by -0.99mmHg (95% CI;-1.61 to -0.37).
- There was a tendency towards an increased BP sensitivity to calcium in populations with a low initial calcium intake (≤800 mg/day) compared to populations with higher intakes (≥800 mg/day), both for systolic BP, -2.68 mmHg (95% CI;-4.07 to -1.28 mm Hg) for the ≤800 mg/day calcium versus - 0.90 mmHg (95% CI; -2.41 to 0.61 mm Hg) for the ≥800 mg/day calcium, respectively and diastolic BP, -1.30mmHg 95% CI ; -2.15 to -0.46 mm Hg) for the ≤800 mg/day calcium versus -0.63mmHg (95% CI; -1.53 to 0.28 mm Hg), for the ≥800 mg/day calcium respectively).

This study suggests that an adequate intake of calcium should be recommended for the prevention of hypertension. More research on BP in people with calcium-deficient diets is warranted.

Imdad A and Bhutta ZA did a systematic review to evaluate preventive effect of calcium supplementation during pregnancy on gestational hypertensive disorders and related maternal and neonatal morbidity and .mortality.59 A total of 15 randomized controlled trials were included in this review. The dose of caslcium supplementation ranged from 0.5 to 2 g/day and it was given before 20–32 weeks of gestation and continued till delivery. The results were as shown below:

- Pooled analysis showed that calcium supplementation during pregnancy reduced risk of preeclampsia by 52% [relative risk (RR) 0.48; 95% confidence interval (CI) 0.34 to 0.67] and that of severe pre-eclampsia by 25% (RR 0.75 [95% CI; 0.57 to 0.98]). There was no effect on incidence of eclampsia (RR 0.73 [95% CI; 0.41 to1.27]).
- There was a significant reduction for risk of maternal mortality/severe morbidity (RR 0.80 [95% CI, 0.65 to 0.97]).
- Calcium supplementation during pregnancy was also associated with a significant reduction in risk of pre-term birth (RR 0.76 [95% CI; 0.60 to 0.97]).
- There was an extra gain of 85g in birth weight in the intervention group compared with control (mean difference 85 g [95% CI; 37g to 133g]).
- There was no effect of calcium supplementation on perinatal mortality (RR 0.90 [95% CI; 0.74 to 1.09]).
- There was a statistically non-significant increased risk of urolithiasis in the intervention group compared with control (RR 1.52 [95% CI; 0.06 to 40.67]).

This study suggests that calcium supplementation during pregnancy is associated with a reduction in risk of gestational hypertensive disorders and pre-term birth and an increase in birth weight. Results of this review suggested the efficacy of calcium supplementation in reducing gestational hypertensive disorders in populations with low calcium intake. Future studies should include consideration of dietary intake of calcium in particular populations and availability of fortified foods.

### Magnesium

(Subjects: Hypertensive patients)

Jee SH et al did a systematic review which included 20 studies consisting of 14 studies on hypertensive patients and 6 studies on normotensive persons totaling 1220 participants.[60] The doses of magnesium given as intervention ranged from 10 to 40 mmol/day (median, 15.4 mmol/day). The results showed that:

- Magnesium supplementation resulted in only a small overall reduction in BP. The pooled net estimates of BP change were -0.6 mm Hg (95% CI; -2.2 to 1.0 mm Hg) for systolic BP and -0.8 mm Hg (95% CI; -1.9 to 0.4 mm Hg) for diastolic BP.
- However, there was an apparent dose-dependent effect of magnesium, with reductions of 4.3 mm Hg systolic BP (95% CI; 6.3 to 2.2 mm Hg; *P<0*.001) and of 2.3 mm Hg diastolic BP (95% CI; 4.9 to 0.0 mm Hg; *P =0* .09) for each 10 mmol/day increase in magnesium dose.

This study suggests a dose-dependent BP reduction from magnesium supplementation. However, adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm this relationship.

### Garlic

(Subjects: Hypertensive patients)

Ried K et al did a systematic review to investigate the effect of garlic preparations on blood pressure.[61] Most studies included in this review used garlic powder dosages of 600–900 mg per day, providing potentially 3.6–5.4 mg of allicin. Twenty five studies were included in this review whereby eleven RCT's were included in the meta analysis consisting of 482 patients. The results were as shown below:

- Meta-analysis of ten studies of the effect of garlic on SBP showed a significant difference between garlic and control groups, with garlic having a greater effect in reducing SBP than placebo by 4.56 mm Hg (95% CI; - 7.36 to -1.77) mm Hg compared with placebo ($p < 0.001$).

- Subgroup analysis of studies with mean SBP in the hypertensive range at start of intervention revealed a greater SBP reduction in the garlic group than placebo by 8.38 mm Hg (95% CI, -11.13 to -5.62 mm Hg) ($p < 0.001$).

- Meta-analysis of eleven studies of the effect of garlic on DBP did not show a significant difference between garlic and placebo groups, -2.44 mm Hg ([95% CI; -4.97 to 0.09mm Hg, $p = 0.06$).

- However, subgroup analysis of studies with mean DBP in the hypertensive range at the start of treatment revealed a significant difference between garlic and control groups. The results indicate that garlic was more effective in reducing DBP than placebo in hypertensive individuals by 7.27 mm Hg (95% CI; -8.77 to -5.76 mm Hg ; $p < 0.001$).

This meta-analysis suggests that garlic preparations may be useful in reducing blood pressure in individuals with hypertension. Future large scale long-term trials are needed to investigate whether standardised garlic preparations could provide a safe alternative or complementary treatment option for hypertension in clinical practice.

## SAFETY

### Vitamin C and E
(Subjects: Pregnant hypertensive patients)

Spinnato II JA et al did a randomized controlled trial from 2003 to 2006 to study whether antioxidant (vitamin C and E) supplementation will reduce the incidence of preeclampsia among patients at high risk.[62] Women between 12 weeks and 19 weeks of gestation and diagnosed to have chronic hypertension or a prior history of preeclampsia were randomly assigned to daily treatment with both vitamin C (1,000 mg) and vitamin E (400 International Units) (n=371) or placebo (n=368). At the same time patients continue with their usual routine antihypertensive care. The women were followed at routine prenatal visits, typically every 4 weeks until 26 to 28 weeks of gestation, every 2 to 3 weeks until 36 weeks of gestation, and then weekly until delivery or the onset of preeclampsia.

- Outcome data for 707 of 739 randomly assigned patients revealed no significant reduction in the rate of preeclampsia (vitamin C and E), 13.8% [49 of 355] compared with placebo, 15.6% [55 of 352], adjusted risk ratio 0.87 [95% CI; 0.61–1.25]).

- There were no (vitamin C and E compared with placebo) differences in the frequency of gestational diabetes (3.4% compared with 3.7%), abruptio placentae (1.1% compared with 2.3%), induction of labor (14.6% compared with 18.3%) or cesarean delivery (66.0% compared with 67.6%). Premature rupture of the membranes was more frequently observed in the vitamin C and E group (10.6% compared with 5.5%, *P=0*.015, RR 1.89, 95% CI; 1.11–3.23).

- Among patients without chronic hypertension, there was a slightly higher rate of severe preeclampsia in the vitamin C and E (vitamin C and E group, 6.5% [11 of 170] compared with placebo, 2.4% [4 of 168], P *=0.*11, odds ratio 2.78 (95% CI; 0.79 –12.62).

Hence, this trial failed to demonstrate a benefit of antioxidant supplementation in reducing the rate of preeclampsia among patients with chronic hypertension.

Spinnato II JA et al did a randomized controlled trial from 2003 to 2006 to determine if antioxidant (vitamin C and E) supplementation during pregnancy on hypertensive patients reduces the incidence of premature rupture of the membranes (PROM).[63] This clinical trial was conducted as a protocol within the National Institute of Child Health and Human Development (NICHD) Global Network for Women's and Children's Health Research. The trial enrolled women seeking prenatal care who were 12 to 19 weeks' pregnant and diagnosed with non-proteinuric chronic hypertension or a prior history of preeclampsia in their most recent pregnancy that progressed beyond 20 week's gestation. They were from major teaching hospitals such as the primary clinical center (Recife) and three additional clinical sites (Campinas, Botucatu, and Porto Alegre). Women were assigned randomly to receive daily vitamin C 1000 mg and vitamin E 400 IU (n=371) or placebo (n=368). All clinicians and clinical investigators were blinded to group assignment. The results showed that:

- Outcome data for premature rupture of the membranes (PROM) were available for 697 of 739 patients. The rates of PROM was 37/349 [10.6%] versus 19/348 [5.5%]; adjusted risk ratio [RR] 1.89 ([95% CI; 1.11to 3.23]; p=0.015).
- And results of PPROM (preterm PROM which is prior to 37 weeks of gestation) was (16/349 [4.6%] versus 6/348 [1.7%]; RR 2.68 [95% CI; 1.07 to 6.71]; p=0.025) were increased in the antioxidant vitamin group.

Contrary to expectations, vitamins C and E supplementation in this dose combination may be associated with an increased risk of PROM and PPROM.

## COST/ COST EFFECTIVENESS

There was no retrievable scientific evidence on the cost/ cost-effectiveness of nutraceuticals to complement therapy for hypertension.

## DISCUSSION

Torres MRSC and Sanjuliani AF in their narrative review mentioned that an inverse relationship between calcium and/or dairy intake and blood pressure has been reported in various epidemiological studies, typically showing that reduced intake of calcium is associated with higher blood pressure and/or an increased risk of developing hypertension.[64-68] The randomized clinical trials that have evaluated the effects of calcium supplementation have identified modest reductions in blood pressure. [67-68]

Cunha AR et al in their narartive review mentioned that magnesium is a mineral with important functions in the body, and it is important that their levels are adequate.[69] The conflicting results of studies evaluating the effects of magnesium supplements on BP and other cardiovascular outcomes indicate that the action of magnesium in the vascular system is present but not yet established.[69] Lack of definitive conclusions due to heterogeneity of study populations with different clinical profiles and severity of illness, lack of standardization of the type of supplement and the dose, and, finally, very short time of treatment, most often between one and three months, are factors that contribute to the difficulty to establish the efficacy of magnesium supplementation for hypertensive patients. Further studies are needed to evaluate the risk of magnesium deficiency and the effects to be considered in this mineral supplementation.

VanBommel E and Cleophas T. suggested in their study that potassium supplementation reduces the BP substantially in hypertensive patients with salt-rich diets.[70] the difference in magnitude of blood pressure reduction between different studies is probably related to the amount of salt intake. Patients with reduced salt intake benefit little from potassium treatment.[70] Yang Q et al mentioned in their survey that a higher sodium-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality, and higher sodium intake is associated with increased total mortality in the general US population.[71] Houston MC. in his review reported that dietary potassium intake has been demonstrated to significantly lower BP in a dose-responsive manner in both hypertensive and nonhypertensive patients in observational studies, clinical trials, and several meta-analyses.

At the moment there is insufficient evidence to demonstrate efficacy of individual nutraceuticals and supplements in hypertension management. The various nutraceuticals should standardize the content of active ingredients. Further high quality randomised clinical trials are needed before any nutraceutical can be can be used as an adjunct to diet or medications for hypertensive patients who cannot achieve target of BP control.

## CONCLUSION

### Efficacy / effectiveness of nutraceutical therapy as a complement for hypertension treatment

#### *L-arginine*

- There was good level of evidence to suggest that 4 to 24 gm. /day oral L-arginine supplementation significantly lowers both systolic and diastolic BP.

#### *Calcium*

- There was good level of evidence to suggest that adequate intake of calcium (0.5 to 2 gm. /day) in the form of calcium gluconate, calcium carbonate or calcium citrate may be recommended for the prevention of hypertension. Supplementation of calcium during pregnancy reduced the risk of preeclampsia, risk of maternal mortality/severe morbidity and there was also a reduction in the risk of pre-term birth.

### *Magnesium*

- There was good level of evidence to suggest that there is a dose-dependent BP reduction from magnesium supplementation. However, further trial with adequate sample power will be required to confirm the relation between magnesium and hypertension.

### *Garlic*

- There was good level of evidence to suggest that garlic preparations (600–900 mg per day, providing potentially 3.6–5.4 mg of allicin) may be useful in reducing blood pressure in individuals with hypertension.

## Safety profile of using nutraceutical therapy as a complement to the treatment of hypertension

### Combined vitamin C (1000 mg) and E (400 IU)

- There was good level of evidence to suggest that supplementation of combined vitamin C (1000 mg) and E (400 IU) to pregnant patients with hypertension showed **no significant reduction** in the rate of preeclampsia compared to placebo. Premature rupture of the membranes was more frequently observed in the study vitamin group. Among patients without chronic hypertension, there was a slightly higher rate of severe preeclampsia in the study group compared with placebo. Hence, Vitamins C and E supplementation in this dose combination may be associated with an increased risk of premature rupture of the membranes (PROM) and preterm premature rupture of the membranes (PPROM).

## RECOMMENDATION

Based on the above review:

- Vitamins C (1000 mg) and E (400 IU) supplementation in this dose combination may be associated with an increased risk of premature rupture of the membranes (PROM) and preterm premature rupture of the membranes (PPROM).

Therefore, this combination **is not recommended for pregnant hypertensive** patients.

- An adequate intake of calcium in the form of calcium gluconate, calcium carbonate or calcium citrate has been shown to reduce both systolic and diastolic BP. Calcium supplementation during pregnancy reduced risk of preeclampsia, risk of maternal mortality/severe morbidity, reduction in risk of pre-term birth.

Therefore, calcium in the form of calcium gluconate, calcium carbonate or calcium citrate may be recommended for the prevention of hypertension in appropriate therapeutic doses.

- Oral L-arginine supplementation has been shown to lower both systolic and diastolic BP.

- Garlic preparations may have the potential in reducing blood pressure in individuals with hypertension.

- There was also a dose-dependent BP reduction from magnesium supplementation.

However, since the study trials were small, therefore, more research with larger, high quality randomised clinical trials are recommended to provide more conclusive scientific evidence before Oral L-arginine, garlic preparations and magnesium supplementation can be established as nutraceuticals to be used as a complement therapy for hypertension.

Commercially available nutraceutical products are not standardized and vary in the content of active ingredients. Issues such as bioavailability, bioactivity of metabolites, dose/response and toxicity of bioactive compounds need to be considered when presented as nutraceuticals. Interaction of these nutraceuticals with other drugs or between different nutraceuticals when taken as a cocktail of supplements are areas of concern and more research are needed to provide solid evidence on these issues. Sufficient legislative safeguards are essential on the use of nutraceuticals in Malaysia. Until further evidence is available, health professionals should be alerted to the possibility of adverse effects of nutraceuticals, the potential for harmful interactions with other medications and nutritional imbalances due to overuse. In order to have scientific knowledge about the nutraceuticals, public should be educated, where recommended daily doses of these nutraceuticals should be known by each consumer. Hence, several large, well designed, randomized, placebo-controlled studies, powered to detect differences in clinical events, are needed to examine any potential role of nutraceutical therapy as an adjunct to existing treatment paradigms.

## CURRENT INTERNATIONAL REGULATORY STATUS OF NUTRACEUTICALS AND FUNCTIONAL FOODS:

There are many products that have been derived from natural sources and are being marketed as health promoter. Consumers, based on their own research and knowledge, are using these supplements as complementary medicine and for therapy. Regulatory agencies are caught between the lack of explicit guidelines and consumers demand for availability of such compounds with full approval for safety of such products. Regulatory agencies worldwide have taken notice of such demands for two reasons - to reduce health care costs as well to protect consumers from unsafe products.[73]

***Japan***: It was the first to introduce the term "functional foods" in early 1980s. Japanese Ministry of Health and Welfare consulted various government agencies, academics, food processors and advisory committees to define a category of foods, ingredients, with health promoting properties. One of the main reasons for establishing such a category was to reduce the escalating health care costs through regular diet. After lengthy consultation the legislation "*tokutei hokenyo shokuhin*", which in English was translated as "foods for specified health use" (FOSHU), was introduced in 1991. The process of getting an FOSHU status is complex and involves 3-steps-development of a product using approved ingredients, conduct clinical trial and submit documentation to the Ministry of Health and Welfare for evaluation and approval.

***United States of America:*** There is no legislative definition for Functional Foods in the US. In the USA the US Federal Food, Drug and Cosmetics (FD&C) and US Federal Trade Commission (FTC) have jurisdiction over foods. Under a memorandum of understanding (MOU), FD&C is responsible for labelling of product, whereas FTC is responsible for food advertising. However, none has the exclusive authority. Sales, development and health claims of foods fall under three major acts. They are: Nutrition labelling and Education Act (NLEA) of 1990; Dietary Supplementary Health and Education Act (DSHEA) of 1994 and Food and Drug Administration of Modernization of1997.

***Canada****:* As per current Canadian Food and Drug Acts any food that claims to have health benefits would fall into drug category. This limits the development of functional food and nutraceutical products for sale in Canada due to the very restrictive regulatory environment. Health Canada, the regulatory body, has taken steps to modify the acts to address the growing consumer demands for the availability of supplements with health claims. In the *Policy Paper on Nutraceuticals/Functional Foods and Health Claims on Food*, Health Canada made the policy decision that the structure/function and risk reduction claims for foods should be permitted while all others claiming to cure, treat, mitigate or prevent illness should be regulated as drugs.

***The European Union****:* Until recently regulating the dietary supplement has been left with each member country. After a lengthy, highly divisive consultative process, the Food Supplement Directive (Directive 2002/46/EC) was signed into law on July 12, 2002. This legislation harmonises vitamin and mineral regulations in all member countries, the 13 countries that have applied for admission. This legislation establishes a list of minerals and vitamins that can be marketed in all member states, but will prohibit sale of a large number of nutrients currently sold in the United Kingdom and other European countries, because they are not in the list.

***Sweden****:* Since 1990, in consultation with the Swedish Nutrition Foundation (SNF), Sweden has allowed the use of health-related claims in the labelling and manufacturing of foods. In 2001, Sweden extended this generic claim to include product-specific physiological claims under PARNUT. This involves developing a Code with a consensus between industries, consumer groups, researchers and regulators. The Code involves two-step process. First the scientific evaluation with input from SNF and external experts and an evaluation report. The second step is the input from the assessment board for diet-health information. Further information is available at: http:// www.snf.ideon.se / snf /en / rh / Health_claims_FF.htm.

***Israel****:* The Food and Nutrition Service of Israeli's Health Ministry is proposing amendments to its existing food regulations which would allow manufacturers of certain food and supplement products to make claims about health benefits of their products. The amendments are an extension of the rules of the US Food and Drug as listed in Dietary Supplementary Health and Education Act (DSHEA ) and Food and Drug Administration Modernization Act (FDAMA).

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## Appendix 1

**PTK – FM – 02**

### HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
### NUTRITIONAL THERAPY AS A COMPLEMENT FOR DIABETES AND HYPERTENSION

## 1. BACKGROUND INFORMATION

The study of nutrition was initiated as early as the 18th century and by the early 20th century, scientists had found that diseases such as beri beri, rickets, scurvy, and pellagra were associated with certain diets. By 1912, a chemist had found a substance (vitamin B1) that actually prevented beri beri, and he named it "vitamin." Later it was found that these diseases were caused by the lack of specific nutrients namely vitamin B1 (thiamine), vitamin D, vitamin C and vitamin B3 (niacin). Researchers and scientists continue to find out more about how individual nutrients can help prevent and treat diseases.

Globally, magnitude of non-communicable diseases has been rapidly growing and constitutes one of the major public health challenges. In 2008, 63% of global deaths were due to non-communicable diseases. In the United States (2008), 68 million populations were estimated to have hypertension, which increases the risk for the leading causes of death, heart disease and stroke. Similarly, Diabetes Mellitus(DM) epidemic is accelerating in the developing world, with an increasing proportion of affected people is in the younger age groups. In Malaysia, the prevalence of both hypertension and Type 2 DM (T2DM) is also rising as demonstrated in the third National Health and Morbidity Survey whereby hypertension among adult 30 years and above was 43.0% and T2DM of 14.9%, an increase of 30.0% and 79.5% from that of 10 years earlier respectively. These chronic diseases have common risk factors and underlying pathologic mechanisms that may be modified by nutrients.

Nutritional therapies encompass preventive and educational approaches to diet and lifestyle changes including personalized dietary therapy, nutraceutical prescription and lifestyle advice within a functional medicine framework. Nutritional therapist provides a broad range of options from changing one's diet, lifestyle changes/modifications programme and nutritional supplementation with vitamins and minerals in prescribed doses.

Nutritional supplement refers to vitamins, minerals, and other nutrients that are used to support good health and treat illness. Dietary supplements are defined in the United States Dietary Supplement Health and Education as any product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following ingredients: a mineral; a vitamin, a herb or other botanical, an amino acid, a supplement used by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any ingredient described (Dietary, 1994).

Various types of oral nutritional supplements (ONS) are used in practice typically macronutrient supplements which may contain vitamins, trace elements and minerals. It was estimated 40% of people consume nutritional supplements with major type of nutritional supplement appears to be combination of vitamin/ mineral supplements. Similarly in Malaysia the prevalence of consuming nutritional supplements (vitamin-mineral) among university students was 43%. ONS are increasingly being used in the community with significant cost implication to the National Health Service (UK). The use of supplements is believed to increase daily intake of vitamins and minerals beyond what is obtained from food alone and may confer health benefits, including chronic disease prevention.

However, there is inadequate policy on the use of ONS or vitamin-mineral supplements in the treatment of hypertension and diabetes. There is little rigorous scientific information available to guide in selecting the types and dosages of supplements to use for disease prevention and complementary to their treatment for hypertension and DM.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, cost effectiveness and organizational aspects of ONS as a complement for diabetes and hypertension.

## 2. POLICY QUESTION

a) Should oral nutraceuticals be recommended as a complementary therapy in the treatment of diabetes and hypertension?

b) Should oral nutraceuticals be recommended as a supplement in the pre-diabetes and pre-hypertension?

### Research Question

i. Is oral nutraceuticals effective as a complementary therapy in the treatment of diabetes and hypertension?

ii. Is oral nutraceuticals effective as a supplement for pre-hypertension and pre-diabetes?

iii. Is there any adverse events related to oral nutraceuticals?

iv. Is oral nutraceuticals cost-effective compared to usual care?

## 3. OBJECTIVE

1. To undertake a systematic review on the effectiveness or efficacy of using ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

2. To assess the safety and cost effectiveness of ONS (nutritional supplementation in prescribed doses) as a complement in the treatment of pre-diabetes, diabetes, pre-hypertension and hypertension.

# 4. METHODOLOGY

## 4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to Nutritional therapy as a complement for diabetes and hypertension. The following sources will be searched:

i. Databases as follows: MEDLINE, Pubmed, EBM Reviews – Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, HTA Database EBM Reviews – NHS Economic Evaluation Database, EBM Full Text- Cochrane DSR, ACP journal Club and DARE.

ii. Other database ;EMBASE, CINAHL

iii. Additional articles will be identified from reviewing the bibliographies of retrieved articles.

## 4.2 Inclusion and exclusion criteria

### Inclusion criteria

i. Study design: systematic reviews, randomized control trials, trials with surrogate end points. Additional studies such as cohort, case control, cross sectional will also be taken into consideration.

ii. Population: subjects with Diabetes Mellitus (Type 1 DM, Type 2 DM, gestational diabetes), subjects with hypertension, pre-diabetes, pre-hypertension

iii. Intervention:

c. Nutraceuticals for hypertension such as:

i. L. arginine,

ii. Fish oil (EPA50/DHA20),

iii. Co-enzyme Q10,

iv. Vit D3,

v. Mixed tocopherol (vitamin E),

vi. Calcium carbonate,

vii. Magnesium citrate,

viii. Potassium gluconate

d. Nutraceuticals for diabetes such as:
   i. Fish oil (EPA50/DHA20),
   ii. Garcinia Cambogia (standardized to 60% hydroxycitric acid),
   iii. Bitter melon (bitter gourd) (standardized 10% momordica charantia),
   iv. Chromium polynicotinate,
   v. D-alpha tocopherol,
   vi. Gamma tocotrienol,
   vii. Vitamin C (ascorbic acid/ascorbate),
   viii. L- carnitine,
   ix. Alpha lipoic acid,
   x. Magnesium citrate,
   xi. Cinnamon ( cinamomum)
   xii. Fenugreek
   xiii. Selenium from yeast,
   xiv. Vitamin A (beta-carotene),
   xv. Vitamin B1 (thiamine),
   xvi. Vitamin B12 (cyanocobalamine/ cobalamine),
   xvii. Vitamin B6 (pyridoxine)

v. Comparators:
   a. Placebo
   b. Usual care

vi. Outcomes:
   - Efficacy of oral neutraceuticals (vitamins/ mineral etc) to reduce diabetes, pre-diabetes, pre-hypertension or hypertension through glycaemic control, HbA1c, systolic, diastolic pressure
   - Reduction in morbidity related to diabetes, pre-diabetes, pre-hypertension or hypertension with ONS
   - Reduction in micro-vascular or macro-vascular complications, neuropathy, nephropathy, fetal outcomes with ONS
   - All cause mortality and cardiovascular effects
   - Surrogate outcomes or biomarkers
   - Reduction in diabetes or hypertension, pre-diabetes or pre-hypertension mortality with ONS
   - Weighted mean differences, adjusted odd ratios (ORs) and relative risks with 95% confidence intervals (CIs) from individual studies
   - Multivariable adjusted hazard ratios with 95% confidence intervals (CIs) from individual studies
   - Adverse events, safety

vii. Articles from year 2000

**Exclusion criteria**

Raw food and spices (without specific dosages) is excluded because it is classified under naturopathy, patients with lifestyle modification/ diet modification, parentral nutritional supplement.

Based on these inclusion criteria, study selection will be carried out independently by two reviewers. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

## 4.3 Data extraction strategy

The following data will be extracted:

- Details of methods and study population characteristics
- Details of intervention and comparator
- Details of individual outcomes for effectiveness, safety, cost effectiveness
- Details of organizational and legal implications related to the use of ONS

Data will be extracted from included studies by a reviewer using a pre-defined data extraction form and checked by another reviewer. Disagreements will be resolved by discussion. A third person, whose decision is final, will be consulted when disagreements persists after discussion.

## 4.4 Quality assessment strategy

The methodological quality of all relevant articles will be assessed by using Critical Appraisal Skills Programme (CASP) depending on the type of study design. Quality assessment will be conducted by a reviewer and checked by a second reviewer.

## 4.5 Methods of analysis / synthesis

Data on clinical effectiveness, safety, and cost effectiveness will be presented in tabulated format with narrative summaries. A decision on whether to pool efficacy, safety and accuracy outcomes will be taken following the updated search and based on clinical and statistical heterogeneity and the range of outcome measures reported. Data will be pooled using fixed model unless statistical heterogeneity between studies is found, in which case random effect model will be used.

# 5. Report writing

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## Appendix 2

Electronic bibliographic databases searched

1. Medline
2. Science direct
3. Spinger Link
4. Embase
5. Cochrane Central Database of Controlled Trials (CENTRAL)
6. Cochrane Database of Systematic Reviews (CDSR)
7. NHS Database of Abstracts of Reviews of Effectiveness (DARE)
8. NHS Economic Evaluation Database (NHS EED)
9. NHS Health Technology Assessment (HTA) Database
10. Pubmed

## Appendix 3

Other source consulted

1. Wolters Kluwer, Lippincott
2. EBM Reviews
3. Canadian Agency for Drugs and Technologies in Health (CADTH)
4. National Institutes for Health and Clinical Excellence (NICE)
5. International Network of Agencies for Health Technology Assessment (INAHTA)
6. World Health Organisation (WHO)
7. Google Scholar
8. EuroSCAN
9. Australia and New Zealand Horizon Scanning Network
10. Guidelines International Network (G-I-N)
11. ClinicalTrials.gov
12. International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

## Appendix 4

# SEARCH STRATEGIES USED IN THE MAJOR ELECTRONIC BIBLIOGRAPHIC DATABASES

## Medline (Pubmed)

### Diabetes

#1 glucose intolerance
#2 pre diabetes
#3 (#1) OR #2
#4 supplements food
#5 dietary supplements
#6 nutraceutical
#7 nutriceutical
#8 (((#4) OR #5) OR #6) OR #7
#9 (#3) AND #8
#10 fish oils
#11 (#3) AND #8
#12 garcinia cambogia
#13 (#3) AND #12
#14 bitter melon
#15 (#3) AND #14
#16 chromium
#17 (#3) AND #16
#18 d-alpha tocopherol
#21 (#3) AND #18
#22 ((((glucose intolerance)) OR (pre diabetes))) AND (d-alpha tocopherol)
#23 vitamin c
#24 ascorbic acid
#25 (#23) OR #24
#26 (#3) AND #25
#27 l-carnitine
#28 (#3) AND #27
#29 alpha lipoic acid
#30 (#3) AND #29
#31 magnesium citrate
#32 (#3) AND #31
#33 (#3) AND #31 schema: all
#34 cinnamon
#35 (#3) AND #34
#36 fenugreek
#37 (#3) AND #36
#38 selenium from yeast
#39 (#3) AND #38
#40 vitamin a
#41 (#3) AND #40

#42 vitamin b1
#43 (#3) AND #42
#44 vitamin b 12
#45 (#3) AND #44
#46 vitamin b6
#47 (#3) AND #46

## Hypertension

#1 blood pressure
#2 high blood pressure
#3 pre hypertension
#4 ((#1) OR #2) OR #3
#5 supplements food
#6 dietary supplements
#7 nutraceuticals
#8 nutriceutical
#9 (((#5) OR #6) OR #7) OR #8
#10 (#4) AND #9
#13 arginine
#14 monohydrate
#15 (#13) OR #14
#16 (#4) and #15
#19 fish oil
#20 (#4) AND #19
#21 coenzyme
#22 co factor enzyme
#23 (#21) OR #22
#24 (#4) AND #23
#25 vitamin d3
#26 cholecalciferol
#27 (#25) OR #26
#28 (#4) AND #27
#29 tocopherol
#30 vitamin e
#31 (#29) OR #30
#32 (#4) AND #31
#33 calcium carbonate
#34 calcium
#35 (#33) OR #34
#36 (#4) AND #35
#37 magnesium
#38 (#4) AND #37
#39 potassium
#40 (#4) AND #39

## Ovid Medline (R) in-Process & other Non-Indexed citations and Ovid Medline (R) 1948 to present.

**Diabetes**

1. glucose Intolerance.tw.
2. (Prediabetic adj1 State$).tw.
3. Prediabetes.tw.
4. 1 or 2 or 3
5. (Supplement$ adj1 food$).tw.
6. (Dietary adj1 supplement$).tw.
7. Nutraceutical$.tw.
8. Nutriceutical$.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. fish oil$.tw.
12. 4 and 11
13. Garcinia$cambogia.tw.
14. Garcinia.tw.
15. Cambogia.tw.
16. 13 or 14 or 15
17. 4 and 16
18. bitter $gourds.tw.
19. charantia$momordica.tw.
20. 18 or 19
21. 4 and 20
22. Chromium.tw.
23. 4 and 22
24. Alpha$ tocopher?l succinate.tw.
25. 4 and 24
26. Gamma$tocotrienol.tw.
27. Gamma.tw.
28. Tocotrienol.tw.
29. 26 or 27 or 28
30. 4 and 29
31. ascorbic $acid.tw.
32. ascorbic.tw.
33. 31 or 32
34. 4 and 33
35. Carnitine$.tw.
36. 4 and 35
37. Alpha$ lipoic.tw.
38. Lipoic.tw.
39. Tromethamine.tw.
40. Thioctacid.tw.
41. 37 or 38 or 39 or 40
42. 4 and 41
43. Magnesium$ citrate.tw.
44. Magnesium.tw.
45. 43 or 44
46. 4 and 45

47. Cinnamon$adj1 zeylacium.tw.
48. Cinnamon.tw.
49. Zeylacium.tw.
50. Cinnamon$.tw.
51. 47 or 48 or 49 or 50
52. 4 and 51
53. Fenugreek$.tw.
54. Trigonella.tw.
55. Foenumgraecum$.tw.
56. 53 or 54 or 55
57. 4 and 56
58. Selenium.tw.
59. 4 and 58
60. vitamin a.tw.
61. trans retinol.tw.
62. 60 or 61
63. 4 and 62
64. Mononitrate$ thiamine.tw.
65. vitamin b 1.tw.
66. thiamine$.tw.
67. 64 or 65 or 66
68. 4 and 67
69. vitamin b12.tw.
70. cobalamin$.tw.
71. eritron.tw.
72. 69 or 70 or 71
73. 4 and 72
74. vitamin b6.tw.
75. 4 and 74

**Hypertension**

1. hypertension.tw.
2. blood pressures high$.tw.
3. pre-hypertension.tw.
4. 1 or 2 or 3
5. (Supplement$ adj1 food$).tw.
6. (dietary adj1 supplement$).tw.
7. nutraceutical$.tw.
8. nutriceutical$.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. arginine$.tw.
12. monohydrate.tw.
13. 11 or 12
14. 4 and 13
15. fish oil$.tw.
16. 4 and 15
17. coenzyme$.tw.

18. cofactor$enzyme.tw.
19. 17 or 18
20. 4 and 19
21. cholecalciferol$.tw.
22. vitamin d3.tw.
23. 21 or 22
24. 4 and 23
25. tocopherol$.tw.
26. vitaminE.tw.
27. 25 or 26
28. 4 and 27
29. calcium$carbonate.tw.
30. calcium.tw.
31. 29 or 30
32. 4 and 31
33. magnesium.tw.
34. 4 and 33
35. potassium.tw.
36. 4 and 35
37. 9 or 13 or 15 or 19 or 23 or 27 or 31 or 33 or 35
38. 4 and 37
39. limit 38 to (humans and yr="2000 - 2012")

**Others Database**

| | |
|---|---|
| EBM Reviews - Cochrane Central Register of Controlled Trials | |
| EBM Reviews - Database of Abstracts of Review of Effects | Same MeSH, keywords, limits used as per MEDLINE search |
| EBM Reviews - Cochrane database of systematic reviews | |
| EBM Reviews - Health Technology Assessment | |
| PubMed | |
| NHS economic evaluation database | |
| National Horizon Scanning unit | |
| Australia and New Zealand Horizon Scanning Network | |
| INAHTA | |
| FDA | |

## Appendix 5

### DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

***SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)***

## Appendix 6

### EVIDENCE TABLES

This appendix contains the evidence tables with data extracted from the 29 studies included in this HTA report.

The evidence tables are arranged in two parts.

- ❏ Part 1 is the evidence tables on the effectiveness and safety of nutritional therapy for diabetes, prediabetes and gestational diabetes
- ❏ Part 2 is the evidence tables on the effectiveness and safety of nutritional therapy for hypertension, pre-hypertension and gestational hypertension

**1. PART 1**

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (fish oil)**

| | |
|---|---|
| **Bibliographic citation** | 1) Montori VM, Farmer A, Wolan PC and Dinneen SF. Fish oil supplementation in type 2 diabetes, Diabetes Care 2000 23:1407–1415. |
| **Study type** | Systematic review with the objective: To determine the effects of fish oil supplementation on lipid levels and glycemic control in patients with type 2 diabetes. |
| **LE** | I |
| **Number of patients & Patient characteristics** | A total of 823 subjects were included in the 18 trials. Most participants had type 2 diabetes of 5–10 years' duration and were treated with diet or oral hypoglycemic agents. |
| **Intervention** | The dose of fish oil ranged from 3 to 18 g (1.08–5.2 g EPA and 0.3–4.8 g DHA).<br><br>The fish oil was usually given in capsules with the exception of 1 study, in which a liquid form was used |
| **Comparison** | The dose of placebo was matched to the dose of fish oil. The placebo used was a vegetable oil with the exception of 1 study that used a saline solution.<br><br>( Most participants had type 2 diabetes of 5–10 years' duration and were treated with diet or oral hypoglycemic agents.) |
| **Length of follow up** | 6 to 24 weeks |
| **Outcome measures/ Effect size** | ❖ No statistically significant effect was observed for fasting glucose, HbA1c, total cholesterol, or HDL cholesterol. *The overall weighted mean difference (-) for fasting glucose was 0.26 mmol/l (95% CI -0.08 to 0.60) and for HbA1c was 0.15% (-0.08 to 0.37). The overall weighted mean difference (-) for total cholesterol was 0.007 mmol/l (95% CI -0.13 to 0.15.)*<br><br>Fish oil supplementation did not result in any statistically or clinically significant increase in fasting glucose or HbA1c.<br><br>❖ A statistically significant increase in LDL cholesterol was especially noted in the studies recruiting hypertriglyceridemic subjects and using the highest doses of fish oil.<br><br>❖ Meta-analysis of pooled data demonstrated a statistically significant effect of fish oil on lowering triglycerides (-0.56 mmol/l [95% CI -0.71 to -0.41]) and raising LDL cholesterol (0.21 mmol/l [0.02 to 0.41]).<br><br>For the study by Pelikanova et al using normal saline as the placebo:<br>❖ The overall weighted mean difference (-) for fasting glucose was 1.20 mmol/l (95% CI -0.59 to 2.99) and for HbA1c was 0.9% (0.015% to 01.785%). |
| **General comments** | |

**Evidence Table:** **Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question:** **Is nutritional therapy effective for diabetes? (Omega -3 fatty acids also known as n -3 fatty acids (n-3 FAs) – fish oil)**

| | |
|---|---|
| **Bibliographic citation** | 2. Stirban A, Nandrean S, Gotting C, Tamler R, Pop A, Monica Negrean M et al. Effects of n–3 fatty acids on macro- and microvascular function in subjects with type 2 diabetes mellitus. Am J Clin Nutr. First published ahead of print, 2010 as doi: 10.3945/ajcn.2009.28374. |
| **Study type** | RCT: |
| **LE** | I |
| **Number of patients & Patient characteristics** | 34 subjects with type 2 diabetes mellitus |
| **Intervention** | 2 g purified EPA/DHA (termed n-3 FAs) |
| **Comparison** | olive oil (placebo) |
| **Length of follow up** | 6 wk |
| **Outcome measures/ Effect size** | Macrovascular (brachial ultrasound of flow-mediated dilatation; FMD) and microvascular [laser-Doppler measurements of reactive hyperemia (RH) of the hand] function at fasting and 2, 4, and 6 h after a highfat meal (600 kcal, 21 g protein, 41 g carbohydrates, 40 g fat) was measured.<br>❖ Fasting vascular function remained unchanged after n-3 FAs and placebo.<br>❖ After placebo supplementation, a significant decrease in postprandial FMD occurred (maximum decrease in FMD was at 4 h: 38% decrease from fasting value), while supplementation with n-3 FAs resulted in a significant decrease in postprandial FMD (FMD decreased by 13% from the fasting value at 4 h)<br>❖ RH remained unchanged after placebo; whereas it improved significantly n-3 FA supplementation (maximum increase was at 2 h: 27%).<br>❖ Fasting triglycerides did not change significantly with either therapy. Other fasting variables were also unaffected by either therapy: Hb A1C (7.1 ± 0.2% treated group compared with 7.1 ± 0.2% placebo group), total cholesterol (184 ± 6 mg/dL treated group compared with 190 ± 6 mg/dL placebo group), LDL cholesterol (112 ± 5 mg/dL treated group compared with 113 ± 5 mg/dL placebo group), HDL cholesterol (46 ± 2 mg/dL treated group compared with 47 ±2mg/dL placebo group.<br>In subjects with type 2 diabetes mellitus, 6 wk of supplementation with n-3 FAs reduced the postprandial decrease in macrovascular function relative to placebo. Moreover, n-3 FA supplementation improved postprandial microvascular function. These observations suggest a protective vascular effect of n-3 FAs. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (bitter melon)**

| | |
|---|---|
| **Bibliographic citation** | 3. John AJ, Cherian R, Subhash HS and Cherian AM, Evaluation of the efficacy of bitter gourd (momordica charantia) as an oral hypoglycemic agent – a randomized controlled clinical trial Indian J Physiol Pharmacol 2003; 47 (3) : 363–365 |
| **Study type** | Randomised control trial : to evaluate the usefulness of Momordica charantia in mild to moderate type 2 diabetes mellitus |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Consecutive type 2 diabetic patients who attended the medical outpatients with fasting plasma glucose (FBS) of 140–200 mg/dl and post prandial plasma glucose (PPS) of 200–300 mg/dl were recruited to the study. |
| **Intervention** | bitter gourd tablets (26 subjects) Each tablet contained 1 gm of dried fruit and each patient received 2 tablets thrice daily, after meals. All patients were asked to continue their routine anti diabetic treatment, which included dietary modification and oral hypoglycemic agents such as sulfonylureas and biguanides. |
| **Comparison** | Riboflavin was given as placebo, All patients were asked to continue their routine anti diabetic treatment, which included dietary modification and oral hypoglycemic agents such as sulfonylureas and biguanides. |
| **Length of follow up** | 4 weeks |
| **Outcome measures/ Effect size** | The mean values of FBS, PPS and fructosamine after 2 and 4 weeks showed no significant change.<br>❖ The FBS was 150.1±26.9 mg/dl at baseline and 150.0±35.3 mg/dl after 4 weeks in the treatment group while it was 155.8±25.0 mg/dl at baseline and 150.7±35.4 mg/dl after 4 weeks in the placebo group.<br>❖ The PPS was 264.4±32.8 mg/dl at baseline and 230.4±61.2 mg/dl after 4 weeks in the treatment group while it was 253.8±29.4 mg/dl at baseline and 257.6±62.9 mg/dl after 4 weeks in the placebo group.<br>❖ The Fructosamine value was 350.8±56.8 mg/dl at baseline and 319.1±60.7 after 4 weeks in the treatment group while it was 349.1±62.0 a mg/dl at baseline and 333.9±64.1 mg/dl after 4 weeks in the placebo group.<br>The present study showed no significant change in blood sugars or fructosamine levels in either treatment or placebo group. The mean drop in blood sugars and serum fructosamine levels in both groups over time was also not significant |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (bitter melon)**

| | |
|---|---|
| **Bibliographic citation** | 4. Ooi CP, Yassin Z, Hamid TA. Momordica charantia for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD007845. DOI: 10.1002/14651858.CD007845.pub3. |
| **Study type** | Systematic review To assess the effects of mormodica charantia for type 2 diabetes mellitus. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Four randomised controlled trials with up to three months duration and investigating 479 participants met the inclusion criteria |
| **Intervention** | Any orally administered mono-preparation ofmomordica charantia (MC) in any dose or form. |
| **Comparison** | Placebo or no treatment with or without active medications, such as insulin, oral hypoglycaemic agents or other herbal or nutritional preparations |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | Primary outcomes:<br>❖ Fasting blood glucose levels (FBG)<br>❖ Glycosylated haemoglobin A1c (HbA1c)<br>❖ Adverse effects (e.g. hypoglycaemia)<br><br>There was no statistically significant difference in the glycaemic control with momordica charantia preparations compared to placebo.<br>❖ Change in HbA1c in Dans 2007 0.22% [95% CI, -0.36% to 0.80%]<br>❖ Change in fasting blood glucose: In Dans 2007 0.66 mmol/L [95% CI -1.69 to 3.01 mmol/L ],while in John 2003 -0.70 mg/dL [95% CI; -22.40 to 21.00 mg/ dL ]<br>❖ Postprandial blood glucose: In John 2003, -27.20 mg/dL [95% CI; -65.33 to 10.93 mg/dL ]<br>❖ Change in serum fructosamine: in John 2003 mean difference was -14.80 mol/ L[95% CI; -53.19, 23.59 mol/ L ]<br>When momordica charantia was compared to metformin there was also no significant change in reliable parameters of glycaemic control.<br>❖ Change in serum fructosamine. Fuangchan 2011, 6.60 mol/L [ 95% CI; -9.64, 22.84 mol/L ]<br><br>the published data of Purificacion 2007 reported that the effect of the momordica charantia leaf preparation intervention was comparable with the control intervention of low dose glibenclamide tablets (2.5 mg twice a day),<br><br>No serious adverse effects were reported in any trial. No trial investigated death from any cause, morbidity, health-related quality of life or costs |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (chromium)**

| | |
|---|---|
| **Bibliographic citation** | 5. Balk EM, Tatsioni A, Lichtenstein AH, Lau J, Pittas AG. Effect of Chromium Supplementation on Glucose Metabolism and Lipids. Diabetes Care, *2007* 30:2154–2163. |
| **Study type** | Systematic review To assess the effects of chromium supplementation on glucose Metabolism and lipid levels. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | 41 studies included 1,198 participants. Almost all study participants with diabetes had type 2, although in three studies this was unclear |
| **Intervention** | four different chromium formulations brewer's yeast (1.28–400 µg/day, 10 studies), chromium chloride (50–600 µg/day, 15 studies), chromium nicotinate (200–800 µg/day, 5 studies) and chromium picolinate (60–1,000 µg/day, 15 studies). One study did not describe the chromium Formulation (400 µg/day) |
| **Comparison** | |
| **Length of follow up** | Study duration ranged from 3 weeks to 8 months. |
| **Outcome measures/ Effect size** | Among participants with type 2 diabetes, chromium supplementation improved glycosylated hemoglobin levels by-0.6% (95% CI -0.9 to -0.2) and fasting glucose by -1.0 mmol/l (-1.4 to -0.5) but not lipids.<br>❖ The overall estimate for the effect of supplementation with brewer's yeast on fasting glucose was statistically significant (-1.1 mmol/l [95% CI -1.6 to -0.6])<br>❖ Chromium picolinate had a significant effect on fasting glucose (-0.8 mmol/l [-1.2 to -0.3]). Doses of 400 or 1,000µg/day appear to have had greater effects than lower doses.<br>❖ For chromium chloride, there was no significant effect on fasting glucose (-0.3 mmol/l [95% CI, -0.9 to+0.2]).<br><br>Lipids:<br>❖ The overall estimate of effect for chromium supplementation was nonsignificant for LDL cholesterol (-0.31mmol/l [95% CI,-0.73 to +0.11]).<br>❖ Individual studies found no difference in effect between different chromium formulation doses on HDL cholesterol<br>❖ Overall estimates for the tested chromium supplements were nonsignificant in participants with type 2 diabetes for Triglycerides<br>Among participants with type 2 diabetes, the effects of different chromium formulation on fasting glucose were each significantly different from each other.<br>❖ Studies of brewer's yeast had the greatest net effect (-1.1 mmol/l), followed by.<br>❖ Chromium picolinate (-0.8 mmol/l) and chromium chloride (-0.3 mmol/l).<br>Chromium supplementation significantly improved glycemia among patients with diabetes. However, future studies that address the limitations in the current evidence are needed before definitive claims can be made about the effect of chromium supplementation. |
| **General comments** | Nine studies were funded by the food or supplement industry, 18 were funded by nonindustry sources, and 14 did not report funding source |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Vitamin C)**

| | |
|---|---|
| **Bibliographic citation** | 6. Hui C, Karne RJ, Hall G, Campia U, Panza JA, Cannon III RO, Wang Y et al,. High-dose oral vitamin C partially replenishes vitamin C levels in patientswith Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance*Am J Physiol Heart Circ Physiol* 290:H137-H145, 2006. |
| **Study type** | RCT: investigated effects of high-dose oral vitamin C to alter endothelial dysfunction and insulin resistance in Type 2 diabetes. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Thirty-two diabetic subjects with low plasma vitamin C (<40 μM). All antidiabetic and antihypertensive medications were stopped for 1 wk before subjects were assessed at the beginning and the end of treatment with either vitamin C or placebo. Thus subjects had their medication withdrawn for 1 wk before each glucose clamp and forearm blood flow (FBF) study. |
| **Intervention** | Vitamin C (800 mg/day for 4 wk). |
| **Comparison** | Placebo. ( 500 mg citric acid/25 ml, pH 7.0) |
| **Length of follow up** | 4 weeks |
| **Outcome measures/ Effect size** | Insulin sensitivity (determined by glucose clamp) and forearm blood flow in response to ACh, sodium nitroprusside (SNP), or insulin (determined by plethysmography) were assessed before and after 4 wk of treatment.<br>❖ In the placebo group (*n* = 17 subjects), plasma vitamin C (22± 3 μM), fasting glucose (159 ± 12 mg/dl), insulin (19 ± 7 μU/ml), did not change significantly after placebo treatment.<br>❖ In the vitamin C group (*n* = 15 subjects), basal plasma vitamin C (23± 2 μM) increased to 48 ± 6 μM after treatment, but this was significantly less than that expected for healthy subjects (>80μM).<br>❖ Endothelium-dependent and -independent vascular function was assessed by measuring forearm blood flow (FBF) in response to graded intra-arterial infusions of acetylcholine and sodium nitroprusside (SNP), respectively.<br>❖ No significant changes in fasting glucose (156± 11 mg/dl), insulin (14± 2 μU/ml or forearm blood flow in response to acetylcholine, SNP, or insulin were observed after vitamin C treatment.<br>High-dose oral vitamin C therapy, resulting in incomplete replenishment of vitamin C levels, is ineffective at improving endothelial dysfunction and insulin resistance in Type 2 diabetes. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Vitamin C & E)**

| | |
|---|---|
| **Bibliographic citation** | 7. Gaede P, Poulsen HE, Parving HH, Pedersen O. Double-blind, randomised study of the effect of combined treatment with vitamin C and E on Ibuminuria in Type 2 diabetic patients. Diabet Med. 2001 Sep;18(9):756-60. |
| **Study type** | Randomised control trial : Objective: supplementation of both vitamin C and E in pharmacological doses lowers albumin excretion rate (AER) in Type 2 diabetic patients with persistent micro/macroalbuminuria. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Thirty Type 2 diabetic patients with AER 30-300 mg/24 h were included from the Steno Diabetes centre, Denmark. |
| **Intervention** | vitamin C (1250 mg) and vitamin E (680 IU) per day. Patients were also treated with oral hpoglycaemic agents or insulin or diet.. Patients with BP > 180/ 100 mmHg diuretics calcium antagonist or blockers were given. |
| **Comparison** | Placebo. Patients were also treated with oral hpoglycaemic agents or insulin or diet.. Patients with BP > 180/ 100 mmHg diuretics calcium antagonist or blockers were given. |
| **Length of follow up** | 4 weeks |
| **Outcome measures/ Effect size** | ❖ Combined treatment with vitamin C and E reduced AER by 19% (95% CI 6-34%) (p = 0.04), whereby the urinary albumin excretion rate was 197 mg/24 h (95% CI 114-341 mg/24 h) in the treatment group versus 243 mg/24 h (146-404 mg/24 h) in the control group.<br>❖ No changes were seen in serum creatinine, haemoglobin A1C or blood pressure.<br>❖ Fasting plasma concentrations of vitamin C and E increased in all patients during active treatment (mean vitamin C 79.4 µmol/L (SD 27.8) versus 41.9 µmol/L (SD18.4) in control group and vitamin E 47.0 µmol/L (SD19.8) versus 29.5 µmol/L (SD15.3) in control, P < 0.000001).<br>Short-term treatment with vitamin C and E in pharmacological doses lowers AER in Type 2 diabetic patients with micro/macroalbuminuria. Further long-term, large-scale studies of this albuminuria reducing treatment modality are warranted. |
| **General comments** | |

**Evidence Table : Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Vitamin C & E)**

| | |
|---|---|
| **Bibliographic citation** | 8. McCance DR, Holmes VA, Maresh MJA, Patterson CC, Walker JD, Pearson DWM, Young IA. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. Lancet. 2010 July 24; 376(6736): 259–266. doi: 10.1016/S0140-6736(10)60630-7. |
| **Study type** | Multicentre randomised placebo controlled trial. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Between April, 2003, and June, 2008, 762 womenwomen from 25 UK antenatal metabolic clinics **with type 1 diabetes** preceding pregnancy, presentation between 8 weeks' and 22 weeks' gestation, singleton pregnancy, and age 16 years or older. |
| **Intervention** | 379 women with vitamin supplementation1000 mg vitamin C and 400 IU vitamin E (a-tocopherol) daily until delivery. |
| **Comparison** | 383 placebo – olive oil |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | The primary endpoint was pre-eclampsia, which we defined as gestational hypertension with proteinuria. Analysis was by modified intention to treat. Estimated percentage adherence did not differ between groups (vitamin C, median 95% [IQR 75–100] versus placebo, 96% [74–100]; vitamin E, 93% [78–100] versus placebo, 93% [74–100]).<br>❖ Overall, 127 (17%) women developed pre-eclampsia. Risk of pre-eclampsia did not differ between vitamin and placebo groups<br>❖ Rates of pre-eclampsia did not differ between vitamin (15%, n=57) and placebo (19%, 70) groups (risk ratio 0·81, 95% CI 0·59–1·12).<br>❖ No adverse maternal outcome including delivery after a hypertension-related admission before 34 or 37 weeks<br>❖ There were no significant differences between vitamin and placebo groups for any clinical neonatal outcome including fetal malformation, fetal loss, infant death, or miscarriage.<br>❖ Mean birthweights for both vitamin and placebo groups; risk of birthweights of 2500 g or less (RR 0·82, 95% CI 0·56–1·20) and 4000 g or more (1·25, 0·95–1·64) did not differ between groups.<br>Supplementation with vitamins C and E did not reduce risk of pre-eclampsia in women with type 1 diabetes. |
| **General comments** | |

| | |
|---|---|
| **Bibliographic citation** | 9. Lonn E, Yusuf S, Hoogwerf DB, Pogue J, Yi Q, Zinman, B et al. Effects of Vitamin E on Cardiovascular and Microvascular Outcomes in High- Risk Patients With Diabetes. *Diabetes Care 2002;* 25:1919–1927. |
| **Study type** | randomized clinical trial (factorial) that evaluated the effects of vitamin E supplementation on major CV outcomes and on the development of nephropathy in people with diabetes. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | 3,654 people with diabetes. enrolled people with and without diabetes at high risk for CV events. Patients were eligible if they were 55 years or older, had a history of CV disease (coronary artery disease, stroke, or peripheral arterial disease) or diabetes in the presence of at least one additional CV risk factor (total cholesterol _5.2 mmol/l, HDL cholesterol _0.9 mmol/l, hypertension, defined as use of medication[ s] to treat high blood pressure, or blood pressure at time of recruitment_160 mmHg systolic or _90 mmHg diastolic, known microalbuminuria, or current smoking). |
| **Intervention** | 400 IU vitamin E or with 10 mg ramipril (Alpha tocopherol). Patients still on normal diabetic care |
| **Comparison** | Placebo.<br>Patients still on normal diabetic care |
| **Length of follow up** | 4.5 years |
| **Outcome measures/ Effect size** | The primary study outcome was the composite of myocardial infarction, stroke, or CV death. There was no significant interaction between the study treatments (ramipril and vitamin E) for the primary, secondary and other study outcomes.<br>❖ In the active vitamin E group, 325 /1838 (17.7%) people with diabetes had a primary outcome event that is Composite of myocardial infarction, stroke, or CV death) versus 313 /1816 (17.2%) in the placebogroup (RR 1.03, 95% CI 0.88–1.21).<br>❖ There were no significance differences between the study groups in the rates of MI 212/1838 (11.5%) for treatment group versus 209/1816 (11.5%) for the control group.<br>❖ there were no significance differences between the study groups in the stroke events; 103 subjects (5.6%) in vitamin E group versus 84 subjects (4.6%) in the control group; RR=1.21 (0.91–1.62).<br>❖ there were no significance differences between the study groups on CV death 142 subjects (7.7%) in vitamin E group versus 145 subjects (8.0%) in control group, RR 0.97 (0.77–1.23).<br>❖ there were no significance differences between the study groups on total mortality, 218 (11.9) in vitamin E group versus 232 (12.8) in control group RR= 0.93 (0.77–1.12).<br>❖ Urinary albumin-to-creatinine ratio was measured in 3,574 (97.8%) participants at baseline, in 3,140 (88.9% of those alive) at 1 year, and in 2,740 (85.9% of those alive) at study end.<br>❖ The albumin-to creatinine ratio did not differ significantly between the two study groups at baseline, at 1 year, or at study end. During followup, 361 (9.9%) study participants developed an albumin-to-creatinine ratio >36 mg/mmol and were asked to provide a 24-h urine collection to test for overt nephropathy. Results were available for 308 (85.3%) patients. In the vitamin E arm, 146 (7.9%) study participants developed overt nephropathy versus 131 (7.2%) study participants in the placebo arm (*P*= 0.37). |
| **General comments** | |

| | |
|---|---|
| **Bibliographic citation** | 10. Skyrme-Jones RAP, O'BrienRC, Berry KL, Meredith IA.Vitamin E Supplementation Improves Endothelial Function in Type I Diabetes Mellitus: A Randomized, Placebo-Controlled study; J Am Coll Cardiol 2000;36:94 –102. |
| **Study type** | Randomized clinical trial that evaluated the effects of vitamin E supplementation on endothelial vasodilator function in type 1 diabetes melitus. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Forty-one subjects with type I DM were recruited. |
| **Intervention** | 1,000 IU/day of oral vitamin E (all-*rac*alpha- tocopherol). Patients still on normal diabetic care. |
| **Comparison** | Placebo. Patients still on normal diabetic care. |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | There was no time-dependent change in FMD or in the response to acetylcholine or systemic arterial compliance (SAC) in the placebo group. A significant improvement in endothelium dependent flow-mediated vasodilation in the brachial artery (FMD) (2.6 ± 0.6% to 7.0 ±6 0.7 %,) were observed in those randomized to vitamin E therapy.<br>❖ Systemic arterial compliance was not affected by vitamin E (0.41 ± 0.03 versus. 0.49 ± 0.06 arbitrary compliance units).<br>❖ The change in FMD was related to the change in low density Lipoprotein (LDL) vitamin E content VEC, whereby as the LDL vitamin E increases, so does the magnitude of FMD(r = 0.42, p, 0.05).<br>❖ Reduced oxidative susceptibility after vitamin E supplementation is associated with improved FMD (= 0.64, p≤ 0.0001).<br>Short-term daily oral supplementation with vitamin E improves endothelial vasodilator function (EVF) in both the conduit and resistance vessels of young subjects with type I DM. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Vit E)**

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| **Bibliographic citation** | 11. Milman U, Blum S, Shapira C, Aronson D, Miller-Lotan R et al . Vitamin E Supplementation Reduces Cardiovascular Events in a Subgroup of Middle-Aged Individuals With Both Type 2 Diabetes Mellitus and the Haptoglobin 2-2 Genotype: A Prospective Double-Blinded Clinical Trial, *Arterioscler Thromb Vasc Biol.* 2008;28:341-347; doi: 10.1161/ATVBAHA.107.153965. |
| **Study type** | RCT: To investigate whether vitamin E could reduce cardiovascular events in Diabetes Mellitus individuals with the Hp 2-2 genotype, (Haptoglobin (Hp), a major antioxidant protein, is a determinant of cardiovascular events in patients with Type 2 diabetes mellitus (DM). The Hp gene is polymorphic with 2 common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 allelic product.) |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | 1434 DM individuals ≥55 years of age with the Hp 2-2 genotype |
| **Intervention** | Vitamin E (400 U/d), alpha tocopherol. Patients still on normal diabetic care. |
| **Comparison** | Placebo. Patients still on normal diabetic care. |
| **Length of follow up** | 18 months |
| **Outcome measures/ Effect size** | The primary composite outcome was myocardial infarction, stroke, and cardiovascular death.<br><br>At the first evaluation of events (first interim analysis), 18 months after initiating the study, the primary outcome, which is the composite outcome of myocardial infarction, stroke, and cardiovascular death was significantly reduced in individuals receiving vitamin E (2.2%) compared with placebo (4.7%; *P*=0.01) with hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.27 to 0.82, and led to early termination of the study.<br><br>This study suggests that a pharmacogenomic approach may be useful to identify a large subgroup of DM individuals with the Hp 2-2 Genotype who could potentially derive cardiovascular benefit from Vitamin E supplementation. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Acetyl-L-carnitine; (ALC))**

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|---|---|
| **Bibliographic citation** | 12. Sima AAF, Calvani M, Mehra M, Amato A, Acetyl-L-Carnitine Improves Pain, Nerve Regeneration, and Vibratory Perception in Patients With Chronic Diabetic Neuropathy; Diabetes Care 2005; 28:96–101. |
| **Study type** | Double-blind, placebo-controlled, randomized study |
| **LE** | I |
| **Number of patients & Patient characteristics** | Men and nonpregnant women between the ages of 18 and 70 years with Diabetes for >1 year and an HbA1c >5.9% were enrolled.<br><br>28 U.S. and Canadian centers (U.S.-Canadian Study [UCS]) and 34 U.S., Canadian, and European centers (U.S.-Canadian-European Study [UCES]) participated , enrolling a total of 1,346 patients entering into the studies. |
| **Intervention** | Acetyl-L-carnitine; (ALC) at two doses (500 or 1,000 mg) given three times a day (t.i.d.) . Patients still on normal diabetic care. |
| **Comparison** | Placebo. Patients still on normal diabetic care. |
| **Length of follow up** | For 1 year. |
| **Outcome measures/ Effect size** | ❖ Morphometric parameters included total myelinated fiber number, mean fiber size, fiber density, fiber occupancy, and axon-to myelin ratio. These measurements were combined in an O'Brien's average rank score. Data showed significant improvements in sural nerve fiber numbers and regenerating nerve fiber clusters. Morphometric evaluations of sural nerve biopsies revealed a significant increase in the O'Brien rank score for all biopsy parameters in the 500-mg ALC arm (144.1 ± 28.9 vs. 132.6 ± 37.8, *P*=0.027), with a significant increase in fiber numbers (-14 ± 197 versus -98± 352;*P*= 0.049) and a significant increase in regenerating clusters (-3.3 ± 8.0 versus -27.9±9.1; *P*=0.033).<br><br>❖ Pain as the most bothersome symptom showed significant improvement in patients taking 1,000 mg ALC. From *Pain visual analogue scale; the results were* -22.89 ± 28.57 for the ALC 1000 mg group versus -15.11 ± 27.89 in placebo after week 26 and -23.82 ± 31.45 in ALC group versus -12.40 ± 29.11 in placebo group at week 52.<br><br>❖ Vibration perception improved significantly in the fingers in both the 500- and 1,000-mg ALC t.i.d. groups (*P*= 0.040 and *P* =0.010) and in the toes in the 1,000-mgt.i.d. Group (*P* = 0.047).<br><br>These studies suggests that ALC treatment is efficacious in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (L-carnitine)**

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|---|---|
| **Bibliographic citation** | 13. Malaguarnera M, Vacante M, Avitabile T,Malaguarnera M, Cammalleri L, and Motta M. L-Carnitine supplementation reduces oxidized LDL cholesterol in patients with diabetes; Am J Clin Nutr 2009;89:71–6. |
| **Study type** | RCT: to evaluate the efficacy of L-carnitine on the reduction of oxidized LDL cholesterol in patients with type 2 diabetes. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Eighty-one patients with diabetes from Cannizzaro Hospital, Catania, Italy) |
| **Intervention** | 2 g L-carnitine once daily (n = 41) |
| **Comparison** | placebo (n = 40). |
| **Length of follow up** | 3 months |
| **Outcome measures/ Effect size** | At the end of the study period, the L-carnitine-treated patients showed significant improvements compared with the placebo group in the following markers:<br>❖ Oxidized LDL levels decreased by 15.1 U/L in L-carnitine group compared with 3.0 U/L in placebo group (P< 0.001);<br>❖ LDL cholesterol decreased by 0.45 mmol/L in L-carnitine group compared with 0.16 mmol/L in placebo group (P < 0.05); triglycerides decreased by 1.02 mmol/L compared with 0.09 mmol/L in placebo group (P<, 0.001);<br>❖ Apolipoprotein A1 concentrations decreased by 0.12 mg/ dL in L-carnitine group compared with 0.03 mg/ dL in placebo group (P<0.05); apolipoprotein B-100 concentrations decreased by 0.13 mg/ dL in L-carnitine group compared with 0.04 mg/dL in placebo group (P <0.05);<br>❖ Thiobarbituric acid– reactive substance concentrations decreased by 1.92 nmol/mL in L-carnitine group compared with 0.05 nmol/mL in placebo group (P<0.001), and conjugated diene concentrations decreased by 0.72 µmol/mL in L-carnitine group compared with 0.110.72 µmol/mL in the placebo group (P , 0.001).<br>❖ No significant decrease was observed in the fasting plasma glucose concentrations in either the L-carnitine- or placebo treated groups compared with baseline. In the L-carnitine-treated group, however, there was a significant decrease in Hb A1C of 0.6% (P < 0.001) after 12 week treatment.<br>This study suggests that oral administration of L-carnitine reduces oxidized LDL cholesterol levels in patients with type 2 diabetes. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (alpha lipoic acid)**

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|---|---|
| **Bibliographic citation** | 14. Mijnhout GS, Kollen BJ, Alkhalaf A, leefstra N, and BiloHJG. Alpha Lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials. International Journal of Endocrinology Volume 2012, Article ID 456279,doi:10.1155/2012/456279. |
| **Study type** | systematic review of the literature to evaluate the effects of alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetesmellitus. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | For study selection, the following inclusion criteria were used: (1) RCTs on alpha lipoic acid, (2) a study population consisting of patients with diabetes mellitus and peripheral neuropathic pain, and (3) use of the z (TSS) as the outcome measure. Five RCTs and one meta-analysis were found. The Total Symptom Score (TSS ) was used as the primary outcome measure. |
| **Intervention** | The dosage of alpha lipoic acid ranged from 100 to 1800 mg per day. Intravenous alpha lipoic acid was given for three weeks, and oral administration varied between three weeks and six months. |
| **Comparison** | placebo |
| **Length of follow up** | 3 weeks to 6 months |
| **Outcome measures/ Effect size** | The primary outcome measure in this meta-analysis was the total symptom score (TSS). The TSS is a questionnaire in which the patient is asked to assess the intensity (absent, mild, moderate, severe) and the frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness) resulting in a scaled score in which 0 means no symptoms and 14.64 means that all four symptoms are severe and more or less continuously present . A 30% change on this scale is considered to be clinically relevant (or ≥2 points in patients with a starting score ≤4 points).<br><br>❖ In these studies an average 50% reduction was seen in the TSS with the oral or intravenous administration of at least 600 mg per day. However, when compared to the subjects in the control groups, the reduction in TSS was actually less than the clinically relevant threshold of 30%, as the TSS in the control group also decreased. This was particularly evident in the studies where alpha lipoic acid was administered orally.<br><br>❖ Overall, the pooled standardized mean difference estimated from all trials revealed a reduction in TSS scores of −2.26 (CI: −3.12 to −1.41; *P* =0.00001) in favour of alpha lipoic acid administration. Subgroup analyses of oral administration showed a mean difference of −1.78 (CI: −2.45 to −1.10; *P* = 0.00001) and intravenous administration showed a mean difference of −2.81 (CI: −4.16 to −1.46; *P* = 0.0001). Hence, when given intravenously at a dosage of 600 mg/day over a period of 3 weeks, alpha lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain.<br><br>Caution:<br>Of all reported adverse events, only heart rate and rhythm disorders were observed significantly more frequently in patients treated with alpha lipoic acid compared to patient treated with placebo (6.9% versus 2.7%, *P* 0.047). |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (Cinnamon)**

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|---|---|
| **Bibliographic citation** | 15. Ziegenfuss TN, Hofheins JE, Mendel RW, Landis J, Anderson RA. Effects of a Water-Soluble Cinnamon Extract on Body Composition and Features of the Metabolic Syndrome in Pre-Diabetic Men and Women. Journal of the International Society of Sports Nutrition 2006; 3(2): 45-53. |
| **Study type** | RCT: To determine the effects of supplementation with a water-soluble cinnamon extract (Cinnulin PF®) on body composition and features of the metabolic syndrome. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Twenty-two subjects with prediabetes and the metabolic syndrome (mean ± SD: age, BMI, systolic blood pressure [SBP], fasting blood glucose [FBG]: mean age; 46.0 ± 9.7 y; 33.2 ± 9.3 kg/m$^2$; 133 ± 17 mm Hg; 114.3 ± 11.6 mg/dL) were randomly assigned to supplement their diet with either Cinnulin PF® (500 mg/d) or a placebo for 12-weeks. |
| **Intervention** | Cinnulin PF® (500 mg/d) |
| **Comparison** | Placebo |
| **Length of follow up** | 12 weeks |
| **Outcome measures/ Effect size** | ❖ Subjects in the Cinnulin PF® group had significant decreases in FBG (-8.4%: 116.3 ± 12.8 mg/dL [pre] to 106.5 ± 20.1 mg/dL [post], p<0.01).<br>❖ SBP (-3.8%: 133 ± 14 mm Hg [pre] to 128 ± 18 mm Hg [post], p<0.001).<br>❖ And increases in lean mass (+1.1%: 53.7 ± 11.8 kg [pre] to 54.3 ± 11.8 kg [post], p<0.002) compared with the placebo group.<br>❖ Additionally, within-group analyses uncovered small, but statistically significant decreases in body fat (-0.7%: 37.9 ± 9.2 % [pre] to 37.2 ± 8.9 % [post], p<0.02) in the Cinnulin PF® group.<br>❖ No significant changes in clinical blood chemistries were observed between groups over time.<br>These results showed that Cinnulin PF® supplementation may reduce FBG and SBP, and improving body composition in men and women with the metabolic syndrome and suggest that this spice can reduce risk factors associated with diabetes and cardiovascular diseases. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (cinnamon)**

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|---|---|
| **Bibliographic citation** | 16. Lu T, Shenga H, ,Wu J, Cheng Y, Zhua J, Chen Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutrition Research 2012; 32: 408-412. |
| **Study type** | RCT: To investigate whether cinnamon supplements are able to aid in the treatment of type 2 diabetes by improving blood glucose control. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Total of 66 chinese patients with type 2 diabetes were recruited. All subjects were outpatients from Xuhui Central Hospital, Shanghai. Sixty-nine patients (including 44 women and 25 men with age >48 years) with type 2 diabetes and who had levels of HbA1c greater than 7.0% and FBG greater than 8.0 mmol/L. |
| **Intervention** | Low-dose and high-dose supplementation with cinnamon extract at 120 and 360 mg/d. all subjects took the same kind of prescribed antidiabetic medication. |
| **Comparison** | Placebo. all subjects took the same kind of prescribed antidiabetic medication. |
| **Length of follow up** | 3 months |
| **Outcome measures/ Effect size** | ❖ The levels of HbA1c and FBG were not significantly altered in the placebo group with HbA1c changing from 8.92% to 8.93% and FBG from 8.92 to 8.71 mmol/L and no significant differences between pre- and posttreatment. However, both the HbA1c and FBG levels were significantly reduced in posttreatment in the low- and high-dose groups. The HbA1c level was decreased from 8.90% ± 1.24 to 8.23% ± 0.99 with a reduction of −0.67% (95% CI; −1.09% to −0.25%) in the low dose group and from 8.92% ± 1.35 to 8.00% ± 1.00 in the high-dose group with an average reduction of −0.93% (95% CI; −1.38% to −0.47%).<br>❖ Fasting blood glucose levels were significantly reduced in patients in the low-dose from 9.00 mmol/L ± 1.23 to 7.99 mmol/L ± 1.05 with a reduction of −1.02 mmol/L (−1.61 mmol/L to −0.42 mmol/L) and high-dose groups from 11.21mmol/L ± 2.21 to 9.59 mmol/L ± 1.66 with a reduction of −1.62 mmol/L (95% CI; −2.32 mmol/L to −0.93 mmol/L) , whereas they were not changed in the placebo group from 8.92 mmol/L ± 1.21 to 8.71 mmol/L ± 2.01 with a small reduction of −0.22 mmol/L (95% CI;−1.34 mmol/L to 0.91 mmol/L).<br>❖ The blood triglyceride levels were also significantly reduced in the low-dose group from 2.93 mmol/L ± 2.08 to 2.15 mmol/L ± 1.19 with a reduction of −0.78 mmol/L (95% CI;−1.32 mmol/L to −0.23 mmol/L).<br>❖ The blood levels of total cholesterol, highdensity lipoprotein cholesterol, low-density lipoprotein cholesterol, and liver transaminase remained unchanged in the 3 groups.<br>This study indicates that cinnamon supplementation is able to significantly improve blood glucose control in Chinese patients with type 2 diabetes. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (cinnamon)**

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|---|---|
| **Bibliographic citation** | 17. Leach MJ, Kumar S. Cinnamon for diabetes mellitus. Cochrane Database Syst Rev. 2012;9:CD007170. doi: 10.1002/14651858.CD007170.pub2. |
| **Study type** | Systematic review of RCT. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Ten prospective, parallel-group design, randomised controlled trials, involving a total of 577 participants with type 1 and type 2 diabetes mellitus, were identified. |
| **Intervention** | Oral mono preparations of cinnamon (predominantly Cinnamomum cassia) were administered at a mean dose of 2 g daily, for a period ranging from 4 to 16 weeks. Patients still on normal diabetic care |
| **Comparison** | Placebo. Patients still on normal diabetic care. |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | ❖ The effect of cinnamon on fasting blood glucose level was inconclusive. 8 trials reported data on fasting blood glucose levels for 338 patients. There was no ststistically significant difference in FBGL between cinnamon and placebo ( mean difference -0.83 mmol/L ( 95% CI; -1.67 mmol/L to 0.02 mmol/L P=0.06) 2 trials with 98 patients reported a mean difference of -0.08mmol/L (95% CI ; 0.39 mmol/L to 0.22 mmol/L' P=0.59).<br>❖ No statistically significant difference in glycosylated haemoglobin A1c (HbA1c) whereby six trials reported a difference of -0.06% ( 95% CI; -0.29 % to 0.18% P=0.63.<br>❖ There was no ststistically significant difference on serum insulin whereby 2 trials stated that the mean difference on serum insulin between cinnamon and placebo group was -6.77pmol/L (95% CI; -37.0 pmol/L to 23.46 pmol/L p=0.66).<br>❖ There were insufficient data to pool results for insulin sensitivity.<br>❖ No trials reported health-related quality of life, morbidity, mortality or costs. Adverse reactions to oral cinnamon were infrequent and generally mild in nature.<br>There is insufficient evidence to support the use of cinnamon for type 1 or type 2 diabetes mellitus. Further trials, which address the issues of allocation concealment and blinding, are now required. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (fenugreek)**

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| **Bibliographic citation** | 18. Mitra A and Bhattacharya D.Dose-dependent effects of Fenugreek composite in Diabetes with dislipidaemia. Internet Journal of Food Safety, Vol.8, 2006, p. 49-55. |
| **Study type** | clinical trial-single blind |
| **LE** | II-I |
| **Number of patients & Patient characteristics** | 80 randomly selected newly diagnosed type-2 diabetes patients. Patients were initially divided in 5 groups of 16 each. Group 1 received 25 g, Group 2 received 50 g, Group 3 received 75 g and group 4 received 100 g of fenugreek seeds for 2 months along with 2.5 g of *Tulsi* leaves powder, while Group 5 acted as control. |
| **Intervention** | Daily doses used were 25 g, 50 g, 75 g and 100 g respectively in two equally divided doses given to each group of patients 15 minutes before lunch and dinner (22). The preparations are mixed with 2.5 g of *Tulsi* leaves powder to mask the bitterness of fenugreek and also for synergistic anti-diabetic actions of *Tulsi.* |
| **Comparison** | Normal diet |
| **Length of follow up** | 2 months |

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| **Outcome measures/ Effect size** | ❖ With 25 g/day of Fenugreek total cholesterol (TLC) was reduced from initial value of 229 ± 12 mg/dl to 227 ± 10 mg/dl while the effects of 50 g/day of fenugreek was a reduction from initial value of 233 ± 10 mg/dl to 232 ± 7 mg/dl. These reductions of TLC values were statistically insignificant. With 75 g/day of Fenugreek the TLC values were reduced from 230 ± 7 mg/dl to 224 ± 9 mg/dl, a reduction of 2.88% ($P \leq 0.05$). 100 g/day of Fenugreek caused a decrease of TLC values from 232 ± 9 mg/dl to 219 ± 7 mg/dl, a reduction of 6.18% ($P \leq 0.05$).<br><br>❖ High density Lipoprotein cholesterol (HDLC) values showed that with 25 g/day of Fenugreek, the initial value of 35 ± 4 mg/dl was increased to 38 ± 3 mg/dl, an increase of 8.62% ($P \leq 0.075$). 50 g/day of Fenugreek caused increase of HDLC values from 36 ± 3 mg/dl was increased to 40 ± 5 mg/dl, an increase of 11.12% ($P \leq 0.05$). With 75 g/day of fenugreek dose, HDLC values were increased from 38 ± 5 mg/dl was increased to 44 ± 3 mg/dl, an increase of 15.15% ($P \leq 0.025$). 100 g/day of fenugreek dose caused increase of HDLC values from 34 ± 3 mg/dl to 42 ± 5 mg/dl, an increase of 23.53% ($P \leq 0.25$).<br><br>❖ 25 g/day of Fenugreek caused reduction of low density lipoprotein cholesterol (LDLC) values from 156 ± 9 mg/dl to 154 ± 5 mg/dl, the reduction was statistically insignificant. With 50 g/day of Fenugreek LDLC values was reduced from 160 ± 5 mg/dl to 158 ± 6 mg/dl, the reduction was also statistically insignificant. 75 g/day of Fenugreek caused a decrease of LDLC values from 156 ± 5 mg/dl to 147 ± 5 mg/dl, a reduction of 5.82% ($P \leq 0.075$). With 100 g/day of Fenugreek LDLC values was reduced from 160 ± 5 mg/dl to 147 ± 9 mg/dl, a reduction of 8.15% ($P \leq 0.05$).<br><br>❖ Analyzing triglycerides (TG), 25 g/day of Fenugreek caused reduction of TG values from 180 ± 12 mg/dl to 175 ± 8 mg/dl, the reduction was 2.75% ($P \leq 0.05$). With 50 g/day of Fenugreek TG values was reduced from 185 ± 12 mg/dl to 174 ± 5 mg/dl, the reduction was 5.94% ($P \leq 0.05$). 75 g/day of Fenugreek caused a decrease of TG values from 180 ± 5 mg/dl to 166 ± 6 mg/dl, a reduction of 7.34% ($P \leq 0.025$). With 100 g/day of Fenugreek TG values was reduced from 185 ± 9 mg/dl to 160 ± 12 mg/dl, a reduction of 13.14% ($P \leq 0.025$).<br><br>FBS values showed that with 25 g/day of Fenugreek, the initial value of 184 ± 11 mg/dl was reduced to 176 ± 7 mg/dl, a decrease of 4.08% ($P \leq 0.025$). With 50 g/day of Fenugreek FBS values was reduced from 184 ± 7 mg/dl to 170 ± 7 mg/dl, the reduction was 7.84% ($P \leq 0.05$). 75 g/day of Fenugreek caused a decrease of FBS values from 183 ± 7 mg/dl to 164 ± 5 mg/dl, a reduction of 10.38% ($P \leq 0.05$). With 100 g/day of Fenugreek FBS values was reduced from 185 ± 10 mg/dl to 165 ± 7 mg/dl, a reduction of 10.56% ($P \leq 0.05$). |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy effective for diabetes? (thiamine)**

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| **Bibliographic citation** | 19. Rabbani N, Alam SS, Riaz S, Larkin JR, Akhtar MW et al. High-dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a randomised, double-blind placebo-controlled pilot study. Diabetologia (2009) 52:208–212. DOI 10.1007/s00125-008-1224-4. |
| **Study type** | RCT: To assess whether oral supplements of thiamine could reverse microalbuminuria in patients with type 2 diabetes. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Type 2 diabetic patients (21 male, 19 female) with microalbuminuria were recruited at the Diabetes Clinic, Sheikh Zayed Hospital, Lahore, Pakistan. |
| **Intervention** | 3×100 mg capsules of thiamine per day. usual care (insulin, diet or hypoglycaemic agents (sulfonylureas, metformin & thiazolidinediones). |
| **Comparison** | Placebo – usual care (insulin, diet or hypoglycaemic agents (sulfonylureas, metformin and thiazolidinediones). |
| **Length of follow up** | 3 months |
| **Outcome measures/ Effect size** | ❖ The primary endpoint of this study was effect on urinary albumin excretion (UAE). After the treatment period, patients receiving thiamine therapy had decreased median UAE, with respect to patients receiving the placebo (30.1 mg/24 h in thiamine group versus 35.5 mg/24 h in placebo; p<0.01). UAE was decreased significantly with respect to baseline in the patients treated for 3 months with thiamine (−17.7 mg/24 h;p<0.001) but not in patients treated with placebo.<br>❖ Linear regression of UAE in relation to treatment time indicated that the rate of decrease in UAE was increased about fourfold in patients treated with thiamine with respect to placebo (5.62 versus 1.52 mg/24 h).<br>❖ There was no significant effect of thiamine supplementation on glycaemic control, dyslipidaemia, BP, GFR or markers of vascular dysfunction during the treatment period.<br>In this pilot study, high-dose thiamine therapy produced a regression of UAE in type 2 diabetic patients with microalbuminuria. Thiamine supplements at high dose may provide improved therapy for early-stage diabetic nephropathy. |
| **General comments** | |

**Evidence Table : Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy safe for diabetes? (Alpha Tocopherol)**

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| **Bibliographic citation** | 1.Ward NC, Wu JH, Clarke MW, Puddey IB, Burke V, Croft KD, Hodgson JM. The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. J Hypertens. 2007 Jan;25(1):227-34. |
| **Study type** | RCT: To investigate the effect of alpha-tocopherol and gamma-tocopherol supplementation on 24-h ambulatory blood pressure (BP) and heart rate, vascular function and oxidative stress in individuals with type 2 diabetes. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Fifty-eight individuals with type 2 diabetes. |
| **Intervention** | 500 mg/day RRR-alpha-tocopherol, 500 mg/day mixed tocopherols (60% gamma-tocopherol). Patients also received usual prescribed diabetic medication. |
| **Comparison** | Placebo. Patients also received usual prescribed diabetic medication. |
| **Length of follow up** | 6 weeks |
| **Outcome measures/ Effect size** | Primary endpoints were 24-h ambulatory BP and heart rate, endothelium-dependent and independent vasodilation and plasma and urinary F2-isoprostanes.<br>❖ Treatment with alpha-tocopherol significantly increased systolic BP [7.0 (5.2, 8.8) mmHg, P < 0.0001], diastolic BP [5.3 (4.0, 6.5) mmHg, P < 0.0001], pulse pressure [1.8 (0.6, 3.0) mmHg, P < 0.005] and heart rate [2.0 (0.6, 3.3) bpm, P < 0.005] versus placebo.<br>❖ Treatment with mixed tocopherols significantly increased systolic BP [6.8 (4.9, 8.6) mmHg, P < 0.0001], diastolic BP [3.6 (2.3, 4.9) mmHg, P < 0.0001], pulse pressure [3.2 (2.0, 4.4) mmHg, P < 0.0001] and heart rate [1.8 (0.5, 3.2) bpm, P < 0.01] versus placebo.<br>❖ Treatment with alpha-tocopherol or mixed tocopherols significantly reduced plasma F2-isoprostanes versus placebo, but had no effect on urinary F2-isoprostanes.<br>❖ Endothelium-dependent and independent vasodilation was not affected by either treatment.<br>Ttreatment with either alpha- or mixed tocopherols significantly increased BP, pulse pressure and heart rate in individuals with type 2 diabetes. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for diabetes, pre-diabetes and gestational diabetes**

**Question : Is nutritional therapy safe for diabetes? (Cyanocobalamine – B12)**

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| **Bibliographic citation** | 2. House AA, Eliasziw M, Cattran DC, Churchill DN, Oliver MJ et al. Effect of B- Vitamin Therapy on Progression of Diabetic Nephropathy A Randomized Controlled Trial. *JAMA. 2010;303(16):1603-1609.* |
| **Study type** | RCT: To determine whether B-vitamin therapy can slow progression of diabetic nephropathy and prevent vascular complications. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | 5 university medical centers in Canada conducted between May 2001 and July 2007 of 238 participants who had type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy. |
| **Intervention** | Single tablet of B vitamins containing folic acid (2.5 mg/d), vitamin B6 (25 mg/d), and vitamin B12 (1 mg/d). Patients also received usual prescribed medication |
| **Comparison** | Placebo. Patients also received usual prescribed medication. |
| **Length of follow up** | The mean (SD) follow-up during the trial was 31.9 (14.4) months. |
| **Outcome measures/ Effect size** | ❖ The mean (SD) baseline GFR was 54.7 (29.5) mL/min/1.73 m2. At 36 months, radionuclide glomerular filtration rate (GFR) decreased by a mean (SE) of 16.5 (1.7) mL/min/1.73 m2 in the B-vitamin group compared with 10.7 (1.7) mL/min/1.73 m2 in the placebo group (mean difference, −5.8; 95% confidence interval [CI], −10.6 to −1.1; *P*=.02).<br>❖ There was no difference in requirement of dialysis (hazard ratio [HR], 1.1; 95% CI, 0.4-2.6; *P*=.88).<br>❖ The 36-month risk of a composite outcome, including MI, stroke, revascularization, and all-cause mortality, in the B-vitamin group occurred more often, which was about double that in the placebo group (HR, 2.0; 95% CI, 1.0-4.0; *P*=.04). The 36-month risks of the composite end point was 23.5% (95% CI, 15.0%-32.0%) in the B-vitamin group and 14.4% (95% CI, 6.9%- 21.8%) in the placebo group<br>❖ The baseline mean plasma total homocysteine was 15.5 (5.2) µmol/L. Plasma total homocysteine decreased by a mean (SE) of - 2.2 (0.4) µmol/L at 36 months in the B-vitamin group compared with a mean (SE) increase of 2.6 (0.4) µmol/L in the placebo group resulting in a significant mean difference of −4.8 (95% CI, −6.1 to −3.7; *P< 0*.001, in favor of B vitamins).<br>In this randomized trial of participants with diabetic nephropathy and stages 1 to 3 chronic kidney disease, the use of high doses of B vitamins (containing 2.5 mg/d of folic acid, 25 mg/d of vitamin B6, and1mg/d of vitamin B12) compared with placebo resulted in a greater decrease in GFR and an increase in MI and stroke and suggesting harm to these patients. it would be prudent to discourage the use of high-dose B vitamins as a homocysteine-lowering strategy outside the framework of properly conducted clinical research. |
| **General comments** | |

**PART 2**

**Evidence Table : Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**

**Question : Is nutritional therapy effective for hypertension? (L- arginine)**

| | |
|---|---|
| **Bibliographic citation** | 1. Dong JY, Qin LQ, MD, Zhang Z, Zhao Y, Wang J et al. Effect of Oral L-arginine Supplementation on Blood Pressure. A Meta-analysis of Randomized, Double-blind, Placebo-controlled Trials. Am Heart J. 2011; 162(6):959-965. |
| **Study type** | Systematic review |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | 11 randomized, double-blind, placebo-controlled trials involving 387 participants. |
| **Intervention** | Oral L-arginine intervention ranging from 4 to 24 g/d. |
| **Comparison** | Placebo |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | ❖ Compared with placebo, L-arginine intervention significantly lowered systolic BP by 5.39 mm Hg (95% CI −8.54 to −2.25, *P* = .001) and diastolic BP by - 2.66 mm Hg (95% CI −3.77 to −1.54, *P* < .001).<br><br>Sensitivity analyses restricted to trials with duration of 4 weeks or longer and to trials in which participants did not use antihypertensive medications yielded similar results.<br><br>❖ After excluding two trials that showed large systolic BP reductions in response to L-arginine intervention, there was no heterogeneity (*P* = .59, $I^2$ = 0%), and the combined effect size was −3.34 mm Hg (95% CI −4.93 to −1.86, *P* < .001).<br><br>❖ Restricting analysis to 8 trials with duration of 4 weeks or longer did not change the overall BP estimates (systolic BP −3.96 mm Hg, 95% CI −5.68 to −2.24; diastolic BP -2.62 mm Hg, 95% CI −4.11 to −1.14).<br><br>❖ Restricting analysis to 7 trials in which participants did not use antihypertensive medications yielded similar results (systolic BP −3.92 mm Hg, 95% CI −6.47 to −1.37; diastolic BP −2.50 mm Hg, 95% CI −3.75 to −1.25).<br><br>❖ Additional analyses examining the influence of an individual trial on the combined effect size by omitting one trial in each turn yielded a range from −3.66 (95% CI −5.54 to −1.78) to −5.92 mm Hg (95% CI −9.33 to −2.51) for systolic BP and a range from −2.40 (95% CI −3.55 to −1.26) to −3.20 mm Hg (95% CI −4.68 to −1.73) for diastolic BP.<br><br>This meta-analysis provides further evidence that oral L-arginine supplementation significantly lowers both systolic and diastolic BP. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**

**Question : Is nutritional therapy effective for hypertension? ( calcium)**

| | |
|---|---|
| **Bibliographic citation** | 2. Mierlo LAJV, Arends LR, Streppel MT, Zeegers MPA, Kok FJ, DE Grobbee DE et al. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. Journal of Human Hypertension, 2006; 20, 571–580. doi:10.1038/sj.jhh.1002038. |
| **Study type** | SR: a meta-analysis of randomized controlled trials to determine the effect of calcium supplementation on BP. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | A systematic search for randomized trials of calcium supplementation and BP in non-pregnant subjects was performed in Medline from 1966 to June 2003.<br><br>Seventy-one trials were identified, 40 of which met the criteria for meta-analysis (total of 2492 subjects). |
| **Intervention** | Daily calcium dose from 355 to 2000 mg (mean: 1200 mg, median: 1055 mg). |
| **Comparison** | |
| **Length of follow up** | Duration of intervention ranged from 3 to 208 weeks (median: 9.5 weeks) |
| **Outcome measures/ Effect size** | ❖ Calcium supplementation (mean daily dose: 1200 mg) reduced systolic BP by -1.86mmHg (95% confidence interval: -2.91 to -0.81) and diastolic BP by -0.99mmHg (95% CI;-1.61 to -0.37).<br><br>❖ there was a tendency towards an increased BP sensitivity to calcium in populations with a low initial calcium intake (≤800 mg/day) compared to populations with higher intakes (≥800 mg/day), both for systolic BP, -2.68 mmHg (95% CI;-4.07 to -1.28 mm Hg) for the ≤800 mg/day calcium versus - 0.90 mmHg (95% CI -2.41 to 0.61 mm Hg) for the ≥800 mg/day calcium, respectively and diastolic BP, -1.30mmHg 95% CI ; -2.15 to -0.46 mm Hg) for the ≤800 mg/day calcium versus -0.63mmHg (95% CI; -1.53 to 0.28 mm Hg), for the ≥800 mg/day calcium respectively).<br><br>This study suggests that an adequate intake of calcium should be recommended for the prevention of hypertension. More research on BP in people with calcium-deficient diets is warranted. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**
**Question : Is nutritional therapy effective for hypertension? ( calcium)**

| | |
|---|---|
| **Bibliographic citation** | 3. Imdad A and Bhutta ZA. Effects of Calcium Supplementation during Pregnancy on Maternal, Fetal and Birth Outcomes P*aediatric and Perinatal Epidemiology*, 2012, 26 (Suppl. 1), 138–152. doi: 10.1111/j.1365-3016.2012.01274.x |
| **Study type** | Systematic review: to evaluate preventive effect of calcium supplementation during pregnancy on gestational hypertensive disorders and related maternal and neonatal morbidity and mortality. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | A total of 15 randomised controlled trials were included in this review. |
| **Intervention** | Calcium supplementation ranged from 0.5 to 2 g/day. |
| **Comparison** | Placebo |
| **Length of follow up** | Calcium supplementation in all the included studies was before 20–32 weeks of gestation and continued till delivery. |
| **Outcome measures/ Effect size** | ❖ Pooled analysis showed that calcium supplementation during pregnancy reduced risk of preeclampsia by 52% [relative risk (RR) 0.48; 95% confidence interval (CI) 0.34, 0.67] and that of severe pre-eclampsia by 25% (RR 0.75 [95% CI 0.57, 0.98]). There was no effect on incidence of eclampsia (RR 0.73 [95% CI 0.41, 1.27]).<br>❖ There was a significant reduction for risk of maternal mortality/severe morbidity (RR 0.80 [95% CI 0.65, 0.97]).<br>❖ Calcium supplementation during pregnancy was also associated with a significant reduction in risk of pre-term birth (RR 0.76 [95% CI 0.60, 0.97]).<br>❖ There was an extra gain of 85 g birthweightin the intervention group compared with control (mean difference 85 g [95% CI 37, 133]).<br>❖ There was no effect of calcium supplementation on perinatal mortality (RR 0.90 [95% CI 0.74, 1.09]).<br>❖ There was a statistically non-significant increased risk of urolithiasis in the intervention group compared with control (RR 1.52 [95% CI 0.06, 40.67]).<br>Calcium supplementation during pregnancy is associated with a reduction in risk of gestational hypertensive disorders and pre-term birth and an increase in birthweight. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**

**Question : Is nutritional therapy effective for hypertension? (magnesium)**

| | |
|---|---|
| **Bibliographic citation** | 4. Jee SH, Miller III ER, Guallar E, Singh VK, Appel LJ, and Klag MJ. The Effect of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Clinical Trials. Am J Hypertens 2002;15: 691–696 |
| **Study type** | Systematic Review |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | The 20 studies included 14 of hypertensive and 6 of normotensive persons totaling 1220 participants |
| **Intervention** | The doses of magnesium ranged from 10 to 40 mmol/day (median, 15.4 mmol/day). |
| **Comparison** | |
| **Length of follow up** | The trials varied in length from 3 to 24 weeks, with a median duration of 8.5 weeks. |
| **Outcome measures/ Effect size** | ❖ Magnesium supplementation resulted in only a small overall reduction in BP. The pooled net estimates of BP change were -0.6 mm Hg (95% CI; -2.2 to 1.0 mm Hg) for systolic BP and -0.8 mm Hg (95% CI; -1.9 to 0.4 mm Hg) for diastolic BP.<br>❖ However, there was an apparent dose-dependent effect of magnesium, with reductions of 4.3 mm Hg systolic BP (95% CI; 6.3 to 2.2 mm Hg; *P<0*.001) and of 2.3 mm Hg diastolic BP (95% CI; 4.9 to 0.0 mm Hg; *P =0* .09) for each 10 mmol/day increase in magnesium dose.<br>This study suggests a dose-dependent BP reduction from magnesium supplementation. However, adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm this relationship. |
| **General comments** | |

## Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension

## Question : Is nutritional therapy effective for hypertension? (Garlic)

| | |
|---|---|
| **Bibliographic citation** | 5. Ried K, Frank OR, Stocks NP, Fakler P and Sullivan T. Effect of garlic on blood pressure: A systematic review and meta-analysis. BMC Cardiovascular Disorders 2008, 8:13 doi:10.1186/1471-2261-8-13 |
| **Study type** | Systematic review: To investigate the effect of garlic preparations on blood pressure. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Eleven studies were included in the meta analysis of 482 patients |
| **Intervention** | Dosage of garlic powder ranged between 600 and 900 mg per day, garlic extract 2400 mg/d and Distilled garlic oil |
| **Comparison** | Placebo |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | ❖ Meta-analysis of ten studies of the effect of garlic on SBP showed a significant difference between garlic and control groups, with garlic having a greater effect in reducing SBP than placebo by 4.56 mm Hg (95% CI; - 7.36 to -1.77) mm Hg compared with placebo ($p < 0.001$)<br>❖ Subgroup analysis of studies with mean SBP in the hypertensive range at start of intervention revealed a greater SBP reduction in the garlic group than placebo by 8.38 mm Hg (95% CI, -11.13 to -5.62 mm Hg) ($p < 0.001$)<br>❖ Meta-analysis of eleven studies of the effect of garlic on DBP did not show a significant difference between garlic and placebo groups, -2.44 mm Hg ([95% CI; -4.97 to 0.09mm Hg, $p = 0.06$).<br>❖ However, subgroup analysis of studies with mean DBP in the hypertensive range at the start of treatment revealed a significant difference between garlic and control groups. The results indicate that garlic was more effective in reducing DBP than placebo in hypertensive individuals by 7.27 mm Hg (95% CI; -8.77 to -5.76 mm Hg ; $p < 0.001$)<br>This meta-analysis suggests that garlic preparations may be useful in reducing blood pressure in individuals with hypertension. |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**

**Question : Is nutritional therapy safe for hypertension? (Vitamicn C and E)**

| | |
|---|---|
| **Bibliographic citation** | 1 Spinnato II JA, MD, Freire S, Silva JLPE, Rudge MVC, Martins-Costa S et al. Antioxidant Therapy to Prevent Preeclampsia A Randomized Controlled Trial. Obstet Gynecol 2007; 110:1311–1318) |
| **Study type** | RCT: To study whether antioxidant supplementation will reduce the incidence of preeclampsia among patients at increased risk. |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Conducted at four Brazilian sites. Women between 12 weeks and 19 weeks of gestation and diagnosed to have chronic hypertension or a prior history of preeclampsia were randomly assigned to daily treatment with both vitamin C (1,000 mg) and vitamin E (400 International Units) or placebo.( (371 in treatment froup and 368 in placebo group)). |
| **Intervention** | Vitamin C (1000 mg) and E (400 IU). Patients continue with their usual routine antihypertensive care. |
| **Comparison** | Placebo. Patients continue with their usual routine antihypertensive care. |
| **Length of follow up** | The women were followed at routine prenatal visits, typically every 4 weeks until 26 to 28 weeks of gestation, every 2 to 3 weeks until 36 weeks of gestation, and then weekly until delivery or the onset of preeclampsia. |
| **Outcome measures/ Effect size** | ❖ Outcome data for 707 of 739 randomly assigned patients revealed no significant reduction in the rate of preeclampsia (study drug, 13.8% [49 of 355] compared with placebo, 15.6% [55 of 352], adjusted risk ratio 0.87 [95% CI; 0.61–1.25]).<br>❖ There were no (study drug compared with placebo) differences in the frequency of gestational diabetes (3.4% compared with 3.7%), abruptio placentae (1.1% compared with 2.3%), induction of labor (14.6% compared with 18.3%) or cesarean delivery (66.0% compared with 67.6%). Premature rupture of the membranes was more frequently observed in the study drug group (10.6% compared with 5.5%, *P=0*.015, RR 1.89, 95% CI; 1.11–3.23).<br>Among patients without chronic hypertension, there was a slightly higher rate of severe preeclampsia in the study group (study drug, 6.5% [11 of 170] compared with placebo, 2.4% [4 of 168], P =0.11, odds ratio 2.78 (95% CI; 0.79 –12.62). |
| **General comments** | |

**Evidence Table: Nutritional therapy as a complement for hypertension, pre-hypertension and gestational hypertension**

**Question : Is nutritional therapy safe for hypertension? (Vitamicn C and E)**

| | |
|---|---|
| **Bibliographic citation** | 2. Spinnato II JA, Freire S, Silva JLPE, Rudge MVC, MD4, Martins-Costa S et al. Antioxidant Supplementation and Premature Rupture of the Membranes: A Planned Secondary Analysis. *Am J Obstet Gynecol.* 2008 October; 199(4): 433.e1–433.e8. doi:10.1016/j.ajog.2008.07.011. |
| **Study type** | RCT: To determine if antioxidant supplementation during pregnancy on hypertensive patients reduces the incidence of premature rupture of the membranes (PROM). |
| **LE** | 1 |
| **Number of patients & Patient characteristics** | Women between 12 and 19 weeks of gestation and diagnosed to have chronic hypertension or a prior history of preeclampsia (371 in treatment froup and 368 in placebo group) |
| **Intervention** | Vitamin C (1000 mg) and E (400 IU). Patients continue with their usual routine antihypertensive care |
| **Comparison** | Placebo. Patients continue with their usual routine antihypertensive care. |
| **Length of follow up** | |
| **Outcome measures/ Effect size** | ❖ Outcome data for **premature rupture of the membranes (**PROM) were available for 697 of 739 patients. The rates of PROM 37/349 [10.6%] versus 19/348 [5.5%]; adjusted risk ratio [RR] 1.89 [95.42% confidence interval CI) 1.11, 3.23]; p=0.015),<br>❖ And results of PPROM (**preterm PROM which is prior to 37 weeks of gestation) was** (16/349 [4.6%] versus 6/348 [1.7%]; RR 2.68 [1.07, 6.71];p=0.025) were increased in the antioxidant vitamin group.<br>Contrary to expectations, vitamins C and E supplementation in this dose combination may be associated with an increased risk of PROM and PPROM. |
| **General comments** | |

## Appendix 7

### LIST OF EXCLUDED STUDIES FOR EVIDENCE TABLE


1. Fuangchan A, Sonthisombat P, Seubnukarn T, Chanouan R, Chotchaisuwat P, Sirigulsatien V, et al.Hypoglycemic effect of bitter melon compared with metformin in newly diagnosed type 2 diabetes patients. Journal of Ethnopharmacology 2011; 134(2):422–428.
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