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This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. 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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Background

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 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.

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.

However, there is inadequate policy on the use of oral nutritional supplements or vitamin-mineral supplements or nutraceuticals 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.

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. 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 categorizes nutraceuticals as dietary supplements and therefore, regulation, is not as stringent as for drugs. Nutraceuticals are therefore, widely available

Policy Question

- i. Should oral nutraceuticals be recommended as a complementary therapy in the treatment of diabetes and hypertension?
- ii. Should oral nutraceuticals be recommended as a supplement in the pre-diabetes and pre-hypertension?

Objective

- i. 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.
- ii. 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-

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.

Result 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 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, and 1mg/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 further 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