IJPSR (2013), Vol. 4, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 December, 2012; received in revised form, 21 January, 2013; accepted, 23 March, 2013

IMPACT OF VITAMINS IN PREVENTION OF RISK FACTORS ASSOCIATED WITH TYPE-2 DIABETES MELLITUS

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Keywords:
Type-2 DM, Insulin, Oxidative stress, Inflammation, Micronutrients

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ABSTRACT: Diabetes mellitus is one of the most common metabolic disorders that cause micro and macro vascular complications. Because of additive effects of hyperglycaemia and hyperlipidaemia for cardiovascular disease, serum lipid and glucose level should be closely monitored in diabetes. Chronic Hyperglycaemia resulting from diabetes has profound effects on nearly every system of the body. The toxic effects of hyperglycaemia may result from accumulation of nonenzymatically glycosylated products, increased sorbitol production in tissue, formation of diacylglycerol leading to activation of protein kinase C or by free radical generation. Since type 2 DM is a major public health problem, accounting for significant premature mortality and morbidity, every possible effort should be made to minimize its complications. Studies have shown that diabetes is accompanied by an increased oxidative damage to all the bimolecules. Enhanced oxidative stress contributes to the development of the diabetic complications. Over the last 5 years, a number of large observational studies have suggested an association between the onset of type 2 diabetes and Vitamin deficiencies. As vitamins have important effects on insulin action, serum lipid and glucose and may have impact on a number of pathways which may be of importance in the development of type 2 diabetes. This article reviews the evidence linking role of Vitamins in the prevention of risk factors associated with type 2 diabetes, and suggests current recommendations for supplementation and the most pertinent research on the use of key vitamins in diabetes management.

INTRODUCTION: Type 2 diabetes mellitus (T2DM) is currently considered as a global health problem where about six people die every minute from the disease worldwide. This rate will make T2DM one of the world's most prevalent causes of preventable mortality [1].

T2DM is caused by impaired glucose tolerance (IGT) as a result of insulin resistance and consequent islet β- cell exhaustion, with ensuring insulin deficiency [2]. In individuals with IGT, numerous genetic, host-related, and environmental factors contribute to the progression of insulin resistance in T2DM [3]. The prevalence of type 2 diabetes continues to increase with increasing number of patients at risk

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Article can be accessed online on:
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of serious diabetes-related complications. Having type 2 diabetes increase the risk of a myocardial infarction two times and the risk of suffering a stroke two to four times. It is also a leading cause of blindness, limb amputation and kidney failure [4].

Diabetes is accompanied by severe oxidative stress which is caused by increased oxygen free radical production. Toxic oxygen free radicals have been implicated in the pathogenesis of Diabetes mellitus, and its micro and macro vascular complications[5]. An imbalance which results from an increased production and/or the reduced scavenging of these free radicals leads to a metabolic state of oxidative stress, which consequently leads to tissue damage. Auto glycosylation reactions, alterations in the sorbitol pathway and hyperglycemia have been proposed as some of the mechanisms which are responsible for this increased oxidative stress [5].

Within the last decade, a hypothesis was proposed to explain the pathogenesis of T2DM that connects the disease to a state of subclinical chronic inflammation [6]. The influence of fat is well known, current thinking suggests that abnormal levels of chemokines released by the expanding adipose tissue in obesity activate monocytes and increase the secretion of pro-inflammatory adipokines. Such cytokines in turn enhance insulin resistance in adipose and other tissues, thereby increasing the risk for T2DM [7]. Together, lipid toxicity and low-grade inflammation appear to be major assaults on insulin sensitivity in insulin-responding tissues [8, 56].

Activation of innate immunity promotes various inflammatory reactions that provide the first line of defence the body invokes against microbial, chemical, and physical injury, leading to repair of damage, isolation of microbial infectious threats and restoration of tissue homeostasis [9]. Previous studies have found that appropriate lifestyle intervention and/or drug treatments are effective in delaying or preventing both diabetes and its complications [10].

This article was undertaken in an attempt to evaluate the current knowledge linking various risk factors associated with type 2 diabetes mellitus and role of vitamins in attenuating inflammation, oxidative stress and thereby reducing the risk of T2DM and its complications.

Epidemiology of Type 2 Diabetes: The world prevalence of diabetes in 2010 among adults aged 20-79 years is estimated to 6.4%, affecting 285 million adults[11]. Between 2010 and 2030, there is an expected 70% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries [11]. Each year more than 231,000 people in the United States and more than 3.96 million people worldwide die from diabetes and its complications [12]. This number is expected to increase by more than 50 percent over next decade [4].

Estimated global healthcare expenditures to treat and prevent diabetes and its complications is at least 376 billion US Dollar (USD) in 2010. By 2030, this number is projected to exceed some 490 billion USD[13]. These costs are mainly due to treatment of concomitant CVD [14]. It has been shown in several studies that a clustering of features, such as high plasma glucose, obesity, dyslipidemia (high triglyceride and total cholesterol levels, low high density lipoprotein (HDL) cholesterol levels and hypertension, referred to as insulin resistance or the metabolic syndrome, is a marker of increased risk for the development of type 2 diabetes as well as for CVD [15]. Environmental and lifestyle factors are the main causes of the dramatic increase in type 2 diabetes prevalence [16, 3]. Genetic factors probably identify those most vulnerable to these changes. Furthermore, studies have shown certain ethnic groups to be more susceptible to developing diabetes than others [17]. *Wild et al* [1] ranked the countries with the largest numbers of diabetes (**Table 1**).

Risk factors for Type 2 Diabetes: Many studies have elaborated the associations between several risk factors and the risk of type 2 diabetes. Body mass index (BMI), lipids, hypertension**,** smoking, physical inactivity, low education, dietary patterns, family history, and recently specific genes are also the most frequently documented risk factors for type 2 diabetes [42].

Overweight, BMI and Diabetes: The pathogenesis of T2DM associated with obesity involves abnormal insulin secretion as a consequence of β-cell failure and the development of insulin resistance. Many longitudinal studies have reported that increased BMI is a strong risk factor for type 2 diabetes [19, 24]. A strong positive association between obesity and type 2 diabetes is found both in men [19], and women [19].

TABLE 1: COUNTRIES WITH THE HIGHEST NUMBERS OF ESTIMATED CASES OF DIABETES FOR YEAR 2000 AND 2030

	Year 2000		Year 2030	
Ranking	**Country**	**People with diabetes (in Millions)**	**Country**	**People with diabetes (in Millions)**
01	India	31.7	India	79.4
02	China	20.8	China	42.3
03	U.S.	17.7	U.S.	30.3
04	Indonesia	8.4	Indonesia	21.3
05	Japan	6.8	Pakistan	13.9
06	Pakistan	5.2	Brazil	11.3
07	Russian Federation	4.6	Bangladesh	11.1
08	Brazil	4.6	Japan	8.9
09	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

Obesity is associated with increased risk of developing insulin resistance and type 2 diabetes. In obese individuals adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of the beta cells, the fall in insulin secretion results in failure to control blood glucose level, leading to type 2 diabetes.

Many genes interact with the environment leading to obesity and in some also to diabetes. Many genes have been shown to be involved in determining the whole range of BMI in a population, with each gene only explaining a few hundred gram difference in body weight [20]. Genes responsible for obesity and insulin resistance interact with environmental factors such as increased fat/ calorie intake and decreased physical activity resulting in the development of obesity and insulin resistance followed ultimately by the development of type 2 diabetes [21].

TABLE 2: [22] HEALTHY WEIGHT IN RELATION TO HEIGHT USING BMI

Classification	BMI (Kg/M^2)
Healthy Weight	18.5-24.9
Over Weight	25-29.9
Obesity I	30-34.9
Obesity II	35-39.9
Obesity III	40 or more

Men are at high risk if they have a waist circumference of 94-102 cm (37-40 inches). Women are at high risk if they have a waist circumference of 80-88 cm (31.5-35 inches)

Abnormal Lipid Level and Diabetes: An abnormal blood lipid profile has been reported as a risk factor for type 2 diabetes by several prospective studies [19, 23, 24]. An inverse relationship between HDL cholesterol and risk of type 2 diabetes have been documented in several of these [23, 24]. Some studies found low HDL cholesterol to be a stronger risk factor for type 2 diabetes in women only [39, 48]. Only one previous study measuring non-fasting triglycerides found an independent risk of type 2 diabetes connected to elevated triglyceride levels [19].

High plasma triglycerides and low plasma HDL cholesterol levels are both seen in the insulin resistance syndrome, which is a pre-diabetic state [15], suggesting that non fasting triglycerides and HDL cholesterol levels reflect the degree of insulin resistance. The mechanisms suggested are increased circulating levels of free fatty acids due to increased insulin levels and increased chylomicron-assembly and secretion in the gut, the latter process being a result of localized insulin resistance in the intestine.

Cross sectional studies have shown that high BMI is associated with a higher level of total cholesterol and unfavourable lipids pattern, with low concentrations of HDL cholesterol and high triglycerides concentrations [25]. Longitudinal studies have shown BMI change over time to be positively associated with changes in total cholesterol, triglycerides, and low density lipoprotein (LDL) cholesterol and negatively associated with HDL cholesterol change [26]. Apart from triglycerides, all these lipids have been shown to convey diabetes risk independently of BMI, but how they interact have been little studied.

Hypertension and Diabetes: Several possible factors are likely to be associated between type 2 diabetes and hypertension. A case control studies have shown that hypertension progression is an independent predictor of type 2 diabetes [27]. Studies have shown that markers of endothelial dysfunction

are associated with new-onset of diabetes [28] and endothelial dysfunction is closely related to blood pressure and hypertension [31]. Markers of inflammation such as C-reactive protein have been consistently related to incident of type 2 diabetes [30] and to increasing blood pressure levels [31] suggesting that inflammation might be another explanatory factor for the association between blood pressure, the metabolic syndrome, and incidence type 2 diabetes [32]. In addition evidence from cross sectional and cohort studies suggests strong relationship between blood pressure and BMI and risk of type 2 diabetes [26].

Smoking and Diabetes: Several prospective studies reported that smoking is a risk factor for developing type 2 diabetes [33]. Recently, a meta analysis including 25 prospective studies showed that smoking was associated with a 44% increased risk of diabetes [34]. The association between smoking and type 2 diabetes was stronger for heavy smokers compared with light smokers or former smokers [34]. In addition some studies found an increased risk of type 2 diabetes in the first 2-3 years after smoking cessation [33]. This could be due to a direct effect of nicotine or other components of cigarette smoke on beta cells of the pancreas as suggested by the association of cigarette smoking with chronic pancreatitis and pancreatic cancer [36].

Also, some studies suggest that heavy smokers with evidence of increased systemic inflammation, who gain substantial weight after quitting, are at high risk of developing type 2 diabetes [37]. However over longer follow up, smoking cessation is associated with a reduction in risk of developing type 2 diabetes [38].

Physical inactivity and Diabetes: Physical activity has been shown to be inversely related with obesity and fat distribution, particularly visceral obesity. Studies have shown that physical activity may reduce risk of type-2 diabetes both directly by improving insulin sensitivity and indirectly by producing beneficial changes in body mass and body composition [39]. Longitudinal studies have found physical inactivity to be a strong risk factor for type 2 diabetes [19]. Prolonged television watching as a surrogate marker of sedentary lifestyle was reported to be positively associated with diabetes risk in both men and women [40]. Moderate and vigorous physical activity was associated with a lower risk of type 2 diabetes [24]. Evidence from clinical trials which included physical activity as an integral part of life style interventions suggested that onset of type 2 diabetes can be prevented or delayed by successful lifestyle interventions that included physical activity as a part of this interventions [10]. Physical activity plays an important role in delaying or prevention of development of type 2 diabetes in those at risk both directly by improving insulin sensitivity and reducing insulin resistance, and indirectly by beneficial changes in body mass and body composition [41].

Illiteracy and Diabetes: Previous prospective studies have examined the association between educational attainment and the incidence of diabetes and found that low education is significant predictor of type 2 diabetes [42]. In a cross sectional study of National Population Health Survey found that people with less than high school were almost twice as likely to report having diabetes as those with a bachelor degree or more [43]. Another cross sectional study from the National Health Interview Survey found that women with low education had a higher prevalence of diabetes than the better educated.

Furthermore, the association varied by race/ethnicity and gender, with Whites, Hispanics and women exhibiting a stronger association between education and diabetes than blacks and men [44]. A recent cross sectional study found that type 2 diabetes risks was higher in the least educated who were obese and inactive compared to the more educated [45]. These studies suggest that educational attainment promote an interest in own health and acquisition of knowledge that strongly influence people's ability to reduce risk by successfully adopting a healthier life style.

Dietary pattern and Diabetes: Daily in pattern diet intake has a role on increased weight, central obesity and insulin resistance and causing future development of diabetes. There are growing evidences that an increased level of free fatty acid and more importantly the relative amounts of saturated and unsaturated fatty acids play an important role in development of insulin resistance. Cross sectional epidemiological studies demonstrate positive associations between intake of saturated fat and heyperinsulinemia [46].

Diet with high saturated fat causes decreased the insulin sensitivity that progress to dysfunction of pancreatic beta cells and causes diabetes. Several large prospective cohort studies showed negative association between dietary fiber intake and risk of developing type 2 diabetes [47]. Higher dietary glycemic index has been consistently associated with elevated risk of type 2 diabetes in prospective cohort studies [48]. The relative risk (RR) for type 2 diabetes highest to the lowest glycemic index was; for quintiles 1–5, respectively: 1, 1.15, 1.07, 1.27, and 1.59 (P for trend 0.001), whereas cereal fiber intake was associated with a decreased risk for quintiles 1–5, respectively: 1, 0.85, 0.87, 0.82, and 0.64 (P for trend 0.004) [48].

The possible mechanisms suggested are that insoluble fibre intake was consistently associated with improved insulin sensitivity and decreases risk of type 2 diabetes [49]. Furthermore large observational studies have suggested an association between low vitamin D status or low vitamin D intake and increased incidence of type 2 diabetes [50]. The suggested mechanisms are that vitamin D deficiency may contribute to beta cell dysfunction, insulin resistance and inflammation that may result in type 2 diabetes. The effect of dietary habits has in all these studies been shown to be independent of BMI change.

Genetics and Diabetes: Several studies have found that a genetic component plays an important role in pathogenesis of type 2 diabetes [16]. Several prospective studies and cross sectional studies have reported that positive family history among first degree relatives confers an increased risk of type 2 diabetes and the risk is greater when both parents are affected [51]. A study on twins have demonstrated that concordance estimate for type 2 diabetes is high in monozygotic compared to dizygotic and the rate increases with duration of follow up.

Also, diabetes prevalence varies substantially among different ethnic groups [16], and this observation of substantial variation of disease prevalence across ethnic groups that share a similar environment, supports the idea that genetic factors contribute to disease predisposition [52]. Data from multiple laboratories support that genetic factors predispose to development of type 2 diabetes by reducing insulin sensitivity and insulin secretion which deteriorate in parallel in most human type 2 diabetes cases [52]. Recent studies have identified variants in 11 genes (TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX) to be significantly associated with the risk of type 2 diabetes independently of other clinical risk factors and variants in 8 of these genes were associated with impaired beta-cell function [18].

Among these genes expressed in pancreatic cells and involved in impairment of insulin secretion, the transcription factors 7-like 2 (TCF7L2), is the locus with the highest risk of type 2 diabetes (HR 1.5) [18]. This corresponds to an attributable risk of 25%, due to an average single allele frequency 18-30% in Northern Europeans [53]. Still the value of genetic information decreased by duration of follow up and eventually only increases the receiver operating characteristics (ROC) achieved by clinical risk factors from 0.74 to 0.75 ($p < 0.0001$)[18]. So far genetic information is of interest for research purposes only.

Type 2 Diabetes and role of Vitamin Supplementation: A simple, sensitive and acceptable screening tool is vital in early identification and intervention of type 2 diabetes. A recent study on early detection of type 2 diabetes mellitus in Chinese and Indian adult populations found age, obesity and family history of diabetes to be moderately discriminative for early detection of diabetes with only an ROC of 62% in men and 64% in women [54], clearly showing the need for screening tools incorporating more risk factors. Indeed, exploring the possibility that supplementation with selected micronutrients can attenuate various risk factors and also obesity-related inflammation in order to delay the development of T2DM should be considered alongside existing public health practices to reduce the disease rising rates.

Micronutrients, T2DM and inflammation: The feasibility of modulating innate immunity-related inflammation as an approach for the prevention of T2DM is based on reports that evaluated the efficacy of anti-inflammatory pharmaceutical agents on disease manifestation [7]. A therapeutic strategy for T2DM that would act primary on the inflammatory system has been proposed in the form of salicylates, an anti-inflammatory agent long known to have a hypoglycemic effect [55].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are able to enhance glucose-induced insulin release, improve glucose tolerance, and increase the effect of insulin in patients with T2DM [56].

In humans, treatment with NSAIDs improved various biochemical indices associated with T2DM [57]. With respect to T2DM, the consensus of available information suggests that micronutrient intake modulates the innate immune system [58] and can subsequently influence the predisposition (to and prevention) of disease [58]. By virtue of this observation, the hope is that the outcome of nutritional supplementation can be simply monitored via its modifying action on the levels of inflammatory biomarkers.

Many micronutrients exhibit well-characterized anti-inflammatory or immunomodulatory functions[57]. Vitamins (e.g., D, E, and C), certain fatty acids (e.g., omega-3 fatty acid) and trace elements (e.g., selenium, zinc, copper and iron) are known to improve the overall function of the immune system, prevent excessive expression and synthesis of inflammatory cytokines, and the 'oxidative burst' potential of macrophages [57].

Vitamin B: Vitamin B1 (Thiamine), Vitamin B6 (Pyridoxin), Vitamin B9 (Folic acid) and Vitamin B12 (Cobalamin) are members of vitamin B family. Recently in a pilot scale, placebo-controlled intervention trial, high-dose Vitamin B1 (Thiamine) supplementation of patients with type 2 diabetes mellitus and early stage diabetic nephropathy (microalbuminuria) improved renal function in all patients and produced regression of microalbuminuria in some individuals [59]. High-dose thiamine therapy holds promise as a novel additional treatment for early-stage diabetic nephropathy.

Combination therapy with vitamins B_6, B_9 and B_{12} is a therapeutic intervention to decrease levels of plasma homocysteine and the risk of cardiovascular disease. However, a recent trial found that cosupplementation with these vitamins exacerbated the decline in renal function and increased the risk of vascular disease in patients with diabetic nephropathy. Confidence in this high-dose vitamin supplement is shaken. High concentrations of plasma total homocysteine are known to be associated with the risk of developing diabetes-related cardiovascular disease, nephropathy and proliferative retinopathy.

Cosupplementation of pyridoxine (vitamin B_6), folic acid (vitamin B_9) and vitamin B_{12} has been used to decrease levels of plasma homocysteine and the risk of cardiovascular disease. A study by House *et al* [60] has now shown substantial adverse outcomes associated with high-dose vitamin B_6, B_9 and B_{12} co supplementation in patients with advanced diabetic nephropathy.

In an another trial, the Heart outcomes Prevention evaluation (HOPE-2) study, [61] involved 5,522 patients with vascular disease or diabetes mellitus and found no effect of high dose B_6, B_9 and B_{12} co supplementation on death from cardiovascular disease, whereas the risk of stroke was decreased and the risk of unstable angina requiring hospitalization was increased. The Homocysteinemia in Kidney and end stage renal Disease (HOST) study [62] involved 2,056 patients with advanced kidney disease and found no effect of high-dose vitamin B_6, B_9 and B_{12} supplements on survival or risk of cardiovascular disease-related events.

Previous studies with high-dose pyridoxine treatment of patients with ischemic heart disease [63] and high-dose treatment with the related compound pyridoxamine is so called vitamer as it fulfils the same specific vitamin function in patients with advanced diabetic nephropathy [64] gave no evidence of acceleration of decline in glomerular filtration rate or increased cardiovascular disease events and mortality.

A further factor underlying the association of high-dose vitamin B_6, B_9 and B_{12} supplements and metabolic dysfunction in diabetic nephropathy could be the effect of high-dose folic acid on metabolite transport via the folate transporter 1 (RFC-1). In addition to facilitating transport of folate, RFC-1 is also a transporter of thiamine monophosphate (TMP) and thiamine pyrophosphate (TPP) [65]. Diabetic nephropathy occurs within a background of thiamine (vitamin B_1) deficiency owing to impaired renal reuptake of thiamine.

Plasma thiamine concentrations were inversely linked to plasma soluble vascular cell adhesion protein 1 (sVCAM-1)- a risk marker of cardiovascular disease [66]. Folate binds to and is transported into cells by the RFC-1 transporter [65]. High-dose folic acid supplementation might exacerbate thiamine deficiency at susceptible sites,

such as the kidney and vascular cells in diabetic nephropathy, by competing with TMP and TPP and impairing their uptake into tissues, thereby inhibiting sharing of thiamine metabolites between tissues rich in thiamine and those deficient in it [66]. Preclinical investigations are now required to test this and other possible mechanisms underlying adverse effects of high dose vitamin B_6, B_9 and B_{12} supplementation.

Vitamin C: Vitamin C is an important antioxidant in human, capable of scavenging oxygen derived free radicals. The daily recommended dietary allowance for vitamin C is 75 mg for women and 90 mg for men, with an additional 35 mg for smokers due to the higher metabolic turnover of the vitamin in this group as compared to non-smokers [67]. Ascorbate appears in the urine at intakes of roughly 60 mg/day. However, the results of a depletion/repletion study in healthy young women showed that ascorbate plasma and white blood cell concentrations only saturate at intakes of 200 mg/day or higher [68]. These results suggest that the current dietary recommendations may not provide tissue-saturating ascorbate concentrations [69].

Indeed, epidemiologic findings suggest that serum ascorbic acid deficiency may be relatively common. For example, a recent crosssectional survey of healthy young adults of the Toronto Nutrigenomics and Health (TNH) Study reported that 1 out of 7 individuals are deficient in serum ascorbic acid [70]. Vitamin C has an important role in immune function and various oxidative and inflammatory processes, such as scavenging reactive oxygen species (ROS), preventing the initiation of chain reactions that lead to protein glycation [67] and protecting against lipid peroxidation [67]. The oxidized products of vitamin C, ascorbyl radical and dehydroascorbic acid are easily converted to ascorbic acid by glutathione, NADH or NADPH [67].

For this reason, there has been interest in determining whether vitamin C might be used as a therapeutic agent against the oxidative stress and subsequent inflammation associated with T2DM. A variety of epidemiologic studies have assessed the effect of vitamin C on biomarkers of oxidation, inflammation and/or T2DM risk [71]. A large cross-sectional evaluation of healthy elderly men from the British Regional Heart Study reported that plasma vitamin C, dietary vitamin C and fruit intake were inversely correlated with serum CRP and tissue plasminogen activator [TPA], a biomarker of endothelial dysfunction [70]. However, only plasma vitamin C was inversely associated with fibrinogen levels [71].

A significant inverse association was found between plasma levels of vitamin C and risk of diabetes (OR=0.38, 95% CI=0.28-0.52). In the same study, a similar association was observed between fruit and vegetable intake and T2DM risk (OR=0.78, 95% CI=0.60-1.00) [72]. One randomized, cross-over, double-blind intervention trial reported no improvement in fasting plasma glucose and no significant differences in levels of CRP, IL-6, IL-1 receptor agonist or oxidized LDL after supplementation with 3000 mg/day of vitamin C for 2 weeks in a group of 20 T2DM patients, compared to baseline levels [73]. Chen and colleagues performed a randomized, controlled, double-blind intervention on a group of 32 diabetic subjects with inadequate levels of vitamin C and found no significant changes in either fasting glucose or fasting insulin after intake of 800 mg/day of vitamin C for 4 weeks [74].

On the other hand, Wang and colleagues showed that the red blood cell sorbitol/plasma glucose ratio was reduced after supplementation with 1000 mg/day vitamin C for 2 weeks in a group of eight diabetics, although no differences were found in fasting plasma glucose[75]. Since sorbitol is a product of the pro-oxidative polyol pathway, this observation may suggest an inhibition of the polyol pathway by vitamin C among subjects with diabetes.

Another study has shown that daily intake of ascorbic acid at 2000 mg/day improved fasting plasma glucose, HbA1c, cholesterol levels and triglycerides in 56 diabetics [76]. In agreement, *Paolisso et. al.* found that 1000 mg/day of vitamin C for 4 months improved LDL and total cholesterol, fasting plasma insulin and free radicals, although it did not affect triglycerides or HDL levels in a group of 40 diabetics [77]. Overall, it remains unclear whether vitamin C intake has an effect on factors related to T2DM. Further research and long-term prospective studies are needed to elucidate the role of vitamin C as a modulator of inflammation and T2DM risk, and to evaluate its potential role as a preventive agent at a population level.

Vitamin D: The role of vitamin D in calcium and phosphorus homeostasis and bone metabolism is well understood. However, more recently vitamin D and calcium homeostasis have also been linked to a number of conditions, such as neuromuscular function, cancer, and a wide range of chronic diseases, including autoimmune diseases, atherosclerosis, obesity, cardiovascular diseases, diabetes and associated conditions such as the metabolic syndrome and insulin resistance [57, 58, 80].

In T2DM, the role of vitamin D was suggested from the presence of vitamin D receptors (VDR) in the pancreatic β-islet cells [58]. In these cells, the biologically active metabolite of vitamin D (i.e., 1,25-dihydroxy-vitamin D; 1,25[OH]D)[78] enhances insulin production and secretion via its action on the VDR [58]. Indeed, the presence of vitamin D binding protein (DBP), a major predictor of serum levels of 25(OH)D and response to vitamin D supplementation [79] and VDR initiated several studies demonstrating a relationship between single nucleotide poly-morphisms (SNPs) in the genes regulating VDR and DBP and glucose intolerance and insulin secretion [50].

This further supports a role for vitamin D in T2DM and may explain the reduced overall risk of the disease in subjects who ingest >800 IU/d of vitamin D [80]. However, an alternative, and perhaps related, explanation was recently proposed for the role of vitamin D in T2DM prevention based on its potent immunomodulatory functions [81].

1,25(OH)D modulates the production of the immunostimulatory IL-12 and the immunosuppressive IL-10 [82] and VDRs are present in most types of immune cells [83]. In this respect, supplementation with vitamin D [84] or its bioactive form, 1,25(OH)D [78], improved insulin sensitivity by preventing the excessive synthesis of inflammatory cytokines. This effect of vitamin D on cytokine synthesis is due to its interaction with vitamin D response elements (VDRE) present in the promoter region of cytokine-encoding genes.

This interaction downregulates the transcriptional activities of cytokine genes and attenuates the synthesis of the corresponding proteins[84]. Vitamin D also deactivates NFκB, which transcriptionally up regulates the pro-inflammatory cytokine-encoding genes [85].

Down regulating the expression of NFκB and downstream cytokine genes inhibits β-cell apoptosis and promotes their survival [82]. As reviewed by *Pittas et al* [82], a number of cross-sectional studies in both healthy and diabetic cohorts have shown an inverse association between serum 25(OH)D and glycemic status measures such as fasting plasma glucose, oral glucose tolerance tests, hemoglobin A1c (HbA1c), and insulin resistance as measured by the homeostatic model assessment (HOMAR), as well as the metabolic syndrome [87, 88].

Data from the National Health and Nutrition Examination Survey (NHANES) showed an inverse, dose-dependent association between serum 25(OH)D and diabetes prevalence in non-Hispanic whites and Mexican Americans, but not in non-Hispanic blacks [80, 87]. The same inverse trend was observed between serum 25(OH)D and insulin resistance as measured by HOMA-R, but there was no correlation between serum levels of vitamin D and β-cell function, as measured by HOMA-β [87, 88]. Data from the same cohort also showed an inverse association between 25(OH)D and prevalence of the metabolic syndrome [88].

In prospective studies, dietary vitamin D intake has been inversely associated with incidence of T2DM. For example, data from the Women's Health Study showed that, among middle aged and older women, taking >511 IU/day of vitamin D reduced the risk of developing T2DM, as compared to ingesting 159 IU/day [89]. Furthermore, data from the Nurses Health Study also found a significant inverse correlation between total vitamin D intake and T2DM risk, even after adjusting for BMI, age, and non-dietary covariates [80]. Intervention studies have shown conflicting results about the effect of vitamin D on T2DM incidence.

One study reported that supplementation with 1,25[OH]2D3 for 1 week did not affect fasting glucose or insulin sensitivity in 18 young healthy men [90]. Another study found that, among 14 T2DM patients, supplementing with 80 IU/day of 1 α-OHD3 ameliorated insulin secretion but did not improve glucose tolerance after a 75 g oral load [91]. Yet another study showed that, among 65 middle-aged men who had IGT or mild T2DM and adequate serum vitamin D levels at baseline, supplementation with 30 IU/day of 1-α-OHD3 for 3 months affected

neither fasting nor stimulated glucose tolerance [92]. However, in a cross-over design, 20 diabetics with inadequate vitamin D serum levels who were given 40 IU/day of 1,25-OHD for 4 days had improved insulin secretion, but showed no changes in fasting or stimulated glucose or insulin concentrations [93]. Although the short duration of this cross-over trial may account for the lack of a significant overall effect, the results suggest that improving vitamin D status can modulate factors associated with the development and progression of T2DM. The data from a 2-year-long trial designed to assess the effects of vitamin D3 or 1-α-OHD3 supplementation on bone health in non-diabetic postmenopausal women were analyzed a posterior and found no significant effect on fasting glucose levels [94].

A post-hoc analysis of data from a 3-year trial for bone health showed that daily supplementation with 700 IU of vitamin D3 and 500 mg of calcium citrate malate did not change blood glucose levels or insulin resistance in elderly adults with normal glucose tolerance. These measures, however, were significantly improved in subjects with IGT at baseline [10]. In this trial the effect of fasting glucose levels in the high-risk group (i.e., IGT) was similar to that observed in the Diabetes Prevention Program after an intensive lifestyle intervention or metformin treatment [95]. Taken together, the available information warrants exploring the possibility that vitamin D (alone or in combination with calcium) can be employed in developing population-based strategies for T2DM prevention and control.

Vitamin E: Vitamin E encompasses a group of 8 compounds, including α, β, γ, and δ tocopherols and α, β, γ, and δ tocotrienols, with differing biological activities. Each compound contains a hydroxyl-containing chromanol ring with a varying number and position of methyl groups between the α, β, γ, and δ forms [96]. It is known to have a significant impact on improving a variety of immune functions [97]. Supplementation with vitamin E increases the rate of lymphocyte proliferation by enhancing the ability of T cells to undergo cell division cycles. The effective anti-inflammatory action of vitamin E was substantiated from observations such as the increased expression of the IL-2 gene and IL-1 receptor antagonist and the decreased expression of IL-4 following vitamin E supplementation in animal models.

Furthermore, vitamin E reduced the serum levels of inflammatory factors such as IL-1β, IL-6, TNF-α , PAI-1, and CRP in T2DM patients [94, 99]. Furthermore, vitamin E downregulates NFκB [99], the principal mediator of inflammatory signalling cascade and its potent lipophilic antioxidant effect on internal and external cell membranes as well as plasma lipoproteins, notably LDL. Based on this latter characteristic, studies in both animal models and humans have demonstrated that vitamin E intake blocks LDL lipid peroxidation, prevents the oxidative stress linked to T2DM-associated abnormal metabolic patterns [hyperglycaemia, dyslipidemia, and elevated levels of FFAs], and, subsequently, attenuates cytokine gene expression [97, 99].

Despite these findings, a recent study evaluated the effects of a combination of vitamin C (1000 mg/day) and vitamin E (400 IU/day) for four weeks on insulin sensitivity in untrained and trained healthy young men and concluded that such supplementation may preclude the exercise-induced amelioration of insulin resistance in humans [100]. This may relate to the source of vitamin E used, i.e., α-, β-, γ-, or δ-tocopherol [101].

Overall, the immunomodulatory, anti-inflammatory and anti-oxidative functions of vitamin E strongly support its possible application in designing effective prevention and/or treatment protocols for T2DM [57]. Current practices for diabetes prevention in the general population include lifestyle change, dietary intervention and exercise.

Vitamin E supplementation may further aid in T2DM prevention and control through its anti-oxidant, anti-inflammatory and immunomodulatory properties. It seems reasonable, therefore, to suggest supplementation with vitamin E together with lifestyle change may be combined into a single program to enhance the success and effectiveness of intervention. This strategy could be more efficient in reducing the low-grade inflammation associated with pre-clinical T2DM and, subsequently the disease burden, than when a single approach is considered.

Moreover, such a combined strategy can be introduced in general practice settings and in a population-based fashion with low expenditure and minimal side effects.

CONCLUSION: Understanding diabetes, its risk factors and the measures used to evaluate the progression of the disease can help in controlling the disease. Supplementation of vitamins, lifestyle changes including diet, exercise, smoking cessation, education and reducing stress are the most important elements for successfully avoiding the complications of diabetes. In a chronic disease without a cure, all treatments, conventional medications and alternative therapies, have a role in treating the disease; as a culture with increasing rates of diabetes and a medical system with fewer and fewer effective options left, new ideas and approaches are required.

ACKNOWLEDGMENT: The authors acknowledge work of Josepha Joseph, University of Tromso, Norway and Alaa Badawi et al., licensee In Tech without which the present article would not be so graceful.

REFERENCES:

1. Wild S, Roglic G, Green A, Sicree R and King H: Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. Diabetes Care, May 2004; 27(5):1047-53.
2. Stumvoll M, Goldstein B and Van Haeften T: Type 2 diabetes principles of pathogenesis and therapy. Lancet 2005; 365:1333–1346.
3. Zimmet P, Alberti KG and Shaw J: Global and societal implications of the diabetes epidemic. Nature 2001; 414:782–787.
4. World Health Organization. Fact Sheet No.312: What is Diabetes? Available at: http://www.who.iny/ mediacentre/factsheets/fs312/en/ Accessed on September 5, 2009.
5. Bambolkar S and Sainani GS: The evaluation of oxidative stress in diabetes with or without vascular complications. J Assoc Physicians India 1995; 43:10-12.
6. Pickup JC and Crook MA: Is type II diabetes mellitus a disease of the innate immune system? Diabetologia 1998; 41:1241–1248.
7. King GL: The role of inflammatory cytokines in diabetes and its complications. Journal Periodontology 2008; 79:1527–1534.
8. Bilan PJ, Samokhvalov V, Koshkina A, Schertzer JD, Samaan MC and Klip A: Direct and macrophage-mediated actions of fatty acids causing insulin resistance in muscle cells. Archive Physiology Biochemistry 2009; 115:176–190.
9. Beutler B: Innate immunity an overview. Molecular Immunology 2004; 40:845–859.
10. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM and Walker EA: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346(6):393-403.
11. Shaw JE, Sicree RA and Zimmet PZ: Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87(1):4-14.
12. International Diabetes Federation: Diabetes Atlas. 4th ed. Brusesls. International Diabetes Federation 2009.
13. International Diabetes Federation: Diabetes Atlas. 4th edn. The economic- impact of diabetes.http://www. diabetesatlas.org/content/economic-impactofdiabetes. Accessed on February 4, 2010.
14. Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR and Hanson AM: Predictors of health care costs in adults with diabetes. Diabetes Care 2005; 28(1):59-64.
15. Taskinen MR: Diabetic dyslipidaemia, from basic research to clinical practice. Diabetologia 2003; 46(6):733-49.
16. Diamond J: The double puzzle of diabetes. Nature 2003; 423(6940):599-602.
17. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC and Colditz GA: Ethnicity, obesity, and risk of type 2 diabetes in women. Diabetes Care 2006; 29(7):1585-90.
18. Lyssenko V: The transcription factor 7-like 2 genes and increased risk of type 2 diabetes. An update. Curr Opin Clin Nutr Metab Care 2008; 11(4):385-92.
19. Almdal T, Scharling H, Jensen JS and Vestergaard H: Higher prevalence of risk factors for type 2 diabetes mellitus and subsequent higher incidence in men. Eur J Intern Med 2008; 19(1):40-5.
20. Hebebrand J and Hinney A: Environmental and Genetic Risk Factors in Obesity. Child and Adolesc Psychiatric Clin N Am 2009; 18(1):83-94.
21. Kahn SE, Hull RL and Utzschneider KM: Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444(7121):840-6.
22. Extract from 'Obesity': 2006; NICE clinical guideline-43.
23. Jacobsen BK, Bonaa KH and Njolstad I: Cardiovascular risk factors, change in risk factors over 7 years, and the risk of clinical diabetes mellitus type 2. The Tromso study. J Clin Epidemiol 2002; 55(7):647-53.
24. Njolstad I, Arnesen E and Lund-Larsen PG: Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark Study. Am J Epidemol 1998; 147(1):49-58.
25. Wild SH and Byrne CD: ABC of obesity. Risk factors for diabetes and coronary heart disease. BMJ 2006; 333(7576):1009-11.
26. Czernichow S, Mennen L, Bertrais S, Preziosi P, Hercberg S and Oppert JM: Relationships between changes in weight and changes in cardiovascular risk factors in middle-aged French subjects. Effect of dieting. Int J Obes Relat Metab Disord 2002; 26(8):1138-43.
27. Movahed MR, Sattur S and Hashemzadeh M: Independent association between type 2 diabetes mellitus and hypertension over a period of 10 years in a large inpatient population. Clin Exp Hypertens 2010; 32 (3):198-201.

28. Meigs JB, O'Donnel CJ, Tofler GH, Benjamin EJ, Fox CS and Lipinska I: Hemostatic markers of endothelial dysfunction and risk of incident type 2 diabetes: The Framingham Offspring Study. Diabetes 2006; 55(2):530-7.
29. Gokce N, Holbrook M, Duffy SJ, Demissie S, Cupples LA and Biegelsen E: Effects of race and hypertension on flow-mediated and nitroglycerin-mediated dilation of the brachial artery. Hypertension 2001; 38(6):1349-54.
30. Hu FB, Meigs JB, Li TY, Rifai N and Manson JE: Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 2004; 53(3):693-700.
31. Blake GJ, Rifai N, Buring JE and Ridker PM: Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation 2003; 108(24):2993-9.
32. Ridker PM, Buring JE, Cook NR and Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. An 8-year follow-up of 14 719 initially healthy American women. Circulation 2003; 107(3):391-7.
33. Yeh HC, Duncan BB, Schmidt MIs, Wang NY and Brancati FL: Smoking, smoking cessation, and risk for type 2 diabetes mellitus. Ann Intern Med 2010; 152(1):10-7.
34. Willi C, Bodenmann P, Ghali WA, Faris PD and Cornuz J: Active smoking and the risk of type 2 diabetes: a systematic review and met-analysis. JAMA 2007; 298(22):2654-64.
35. Attvall S, Fowelin J, Lager I, Von SH and Smith U: Smoking induces insulin resistance- -a potential link with the insulin resistance syndrome. J Intern Med 1993; 233(4):327-32.
36. Talamini G, Bassi C, Falconi M, Sartori N, Salvia R and Rigo L: Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. Dig Dis Sci 1999; 44(7):1303-11.
37. Duncan BB, Schmidt MI, Chambless LE, Folsom AR and Heiss G: Inflammation markers predict increased weight gain in smoking quitters. Obes Res 2003; 11(11):1339-44.
38. Wannamethee SG, Shaper AG and Perry IJ: Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001; 24(9):1590-5.
39. Kriska A: Can physically active lifestyles prevent type 2 diabetes, Exercise and sport sciences reviews, Jul 2003; 31(3):132-7
40. Krishnan S, Rosenberg L and Palmer JR: Physical activity and television watching in relation to risk of type 2 diabetes. The Black Women's Health Study. Am J Epidemiol 2009; 169(4):428-34.
41. Kay SJ, Fiatarone and Singh MA: The influence of physical activity on abdominal fat: a systematic review of the literature. Obes Rev 2006; 7(2):183-200.
42. Valdes S, Botas P, Delgado E, Alvarez F and Cadorniga FD: Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. Diabetes Care 2007; 30(9):2258-63.
43. Tang M, Chen Y and Krewski D: Gender-related differences in the association between socioeconomic status and self-reported diabetes. Int J Epidemiol 2003; 32(3):381-5.
44. Borrell LN, Dallo FJ and White K: Education and diabetes in a racially and ethnically diverse population. Am J Public Health 2006; 96(9):1637-42.
45. Dasgupta K, Khan S and Ross NA: Type 2 diabetes in Canada: concentration of risk among most disadvantaged men but inverse social gradient across groups in women. Diabetic Medicine 2010; 27(5):522-31.
46. Dippenaar NG and Haag M: Dietary fats, fatty acids and insulin resistance. Short review of a multifaceted connection 2005; 11(12):RA359-367.
47. Bazzano LA, Serdula M and Liu S: Prevention of type 2 diabetes by diet and lifestyle modification, Journal of the American College of Nutrition 2005; vol 24:5,310-319.
48. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC and Hu FB: Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr 2004; 80(2):348-56.
49. Meyer KA, Kushi LH, Jacobs DR, Jr, Slavin J, Sellers TA and Folsom AR: Carbohydrates, dietary fiber and incident type 2 diabetes in older women. Am J Clin Nutr 2000; 71(4):921-30.
50. Pittas AG, wson-Hughes B, Li T, van Dam RM, Willett WC and Manson JE: Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 2006; 29(3):650-6.
51. Amini M and Janghorban M: Diabetes and impaired glucose regulation in first degree relatives of patients with type 2 diabetes in Isfahan, Iran. Prevalence and risk factors. Rev Diabet Stud 2007; 4:169-176.
52. Swapan Kumar Das and Steven C Elbein: The genetic basis of type 2 diabetes. Cellscience 2006; 2:100-31.
53. Cauchi S and Froguel P: TCF7L2 genetic defect and type 2 diabetes. Curr Diab Rep 2008; 8(2):149-55.
54. Gao WG, Dong YH, Pang ZC; Nan HR, Wang SJ, Ren J, Zhang L, Tuomilehto J and Qiao Q: A simple Chinese risk score for undiagnosed diabetes. Diabet Med 2010; 2 7:274-82.
55. Robertson RP: Prostaglandins as modulators of pancreatic islet function. Diabetes 1979; 28:942–948.
56. Hotamisligil GS: Inflammation and metabolic disorders. Nature 2006; 444:860–867.
57. Badawi A, Klip A, Haddad P, Cole DEC, Bailo BG, El-Sohemy A, and Karmali M: Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. Diabetes Metabolic Syndrome Obesity 2010; 3:173-186.
58. Maggini S, Wintergerst ES, Beveridge S and Hornig DH: Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. British Journal Nutrition 2007; 98(Suppl 1):S29–S35.
59. Rabbani N. *et al*: High dose thiamine therapy for patients with type 2 diabetes and microalbuminuria. A pilot randomised, doubleblind, placebo-controlled study. Diabetologia 2009; 52:208–212.

60. House AA. *et al*: Effect of B-vitamin therapy on progression of diabetic nephropathy. A randomized controlled trial. JAMA 2010; 303: 1603–1609.
61. Lonn, e. *et al*: Homocysteine lowering with folic acid and B vitamins in vascular disease. N. Engl. J. Med 2006; 354: 1567–1577.
62. Jamison, R. L. *et al*: Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and endstage renal disease. A randomized controlled trial. JAMA 2007; 298: 1163–1170.
63. Ebbing M *et al*: Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 2009; 302: 2119–2126.
64. Williams M *et al*: Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. Am. J. Nephrol 2007; 27: 605–614.
65. Zhao R, Gao F and Goldman ID: Reduced folate carrier transports thiamine monophosphate. An alternative route for thiamine delivery into mammalian cells. Am. J. Physiol. Cell Physiol 2002; 282: C1512–C1517.
66. Thornalley PJ: The potential role of thiamine (vitamin B1) in diabetic complications. Curr. Diabetes Rev 2005; 1: 287–298.
67. Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, Folkerts G, Friedmann PS, Frost GS, Guarner F, Lovik M, Macfarlane S, Meyer PD, M'Rabet L and Serafini M: Inflammatory disease processes and interactions with nutrition. British Journal Nutrition 2009; 101 (Suppl 1):S1-S45.
68. Levine M, Wang Y, Padayatty SJ and Morrow J: A new recommended dietary allowance of vitamin C for healthy young women. Proceedings National Academy Science USA 2001; 98:9842-9846.
69. Aguirre R and May JM: Inflammation in the vascular bed: importance of vitamin C. Pharmacological Therapy 2008; 119:96-103.
70. Cahill L, Corey PN and El-Sohemy A: Vitamin C deficiency in a population of young Canadian adults. American Journal Epidemiology 2009; 170:464-471.
71. Wannamethee SG, Lowe GD, Rumley A, Bruckdorfer KR and Whincup PH: Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and haemostasis. American Journal Clinical Nutrition 2006;83:567-574.
72. Harding AH, Wareham NJ, Bingham SA, Khaw K, Luben R, Welch A and Forouhi NG: Plasma vitamin C level, fruit and vegetable consumption, and the risk of new-onset type 2 diabetes mellitus. The European prospective investigation of cancer, Norfolk prospective study. Archives Internal Medicine 2008; 168:1493-1499.
73. Lu Q, Bjorkhem I, Wretlind B, Diczfalusy U, Henriksson P and Freyschuss A: Effect of ascorbic acid on microcirculation in patients with Type II diabetes: a randomized placebo-controlled cross-over study. Clinical Science 2005;108:507-513.
74. Chen H, Karne RJ, Hall G, Campia U, Panza JA, Cannon RO, III, Wang Y, Katz A, Levine M and Quon MJ: High-dose oral vitamin C partially replenishes vitamin C levels in patients with Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. American Journal Physiology Heart Circulation Physiology 2006; 290:H137-H145.
75. Wang H, Zhang ZB, Wen RR and Chen JW: Experimental and clinical studies on the reduction of erythrocyte sorbitol-glucose ratios by ascorbic acid in diabetes mellitus. Diabetes Research Clinical Practice 1995; 28:1-8.
76. Eriksson J and Kohvakka A: Magnesium and ascorbic acid supplementation in diabetes mellitus. Annals Nutrition Metabolism 1995; 39:217-223.
77. Paolisso G, Balbi V, Volpe C, Varricchio G, Gambardella A, Saccomanno F, Ammendola S, Varricchio M and D'Onofrio F: Metabolic benefits deriving from chronic vitamin C supplementation in aged non-insulin dependent diabetics. Journal American College Nutrition 1995; 14:387-392.
78. Anan F, Takahashi N, Nakagawa M, Ooie T, Saikawa T and Yoshimatsu H: High-sensitivity C-reactive protein is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients. Metabolism 2005; 54:552-558.
79. Fu L, Yun F, Oczak M, Wong BY, Vieth R and Cole DE: Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25- hydroxyvitamin D (25(OH)D) to vitamin D supplementation. Clinical Biochemistry 2009; 42:1174-1177.
80. Teegarden D and Donkin SS: Vitamin D: emerging new roles in insulin sensitivity. Nutrition Research Reviews 2009; 22:82-92.
81. Cantorna MT, Zhu Y, Froicu M and Wittke A: Vitamin D status, 1,25-dihydroxy- vitamin D3, and the immune system. American Journal Clinical Nutrition 2004; 80:1717S-1720S.
82. Veldman CM, Cantorna MT and DeLuca HF: Expression of 1,25-dihydroxyvitamin D3 receptor in the immune system. Archive Biochemistry Biophysics. 2000; 374:338.
83. Riachy R, Vandewalle B, Kerr CJ, Moerman E, Sacchetti P, Lukowiak B, Gmyr V, Bouckenooghe T, Dubois M and Pattou F: 1,25-dihydroxyvitamin D3 protects RINm5F and human islet cells against cytokine-induced apoptosis: implication of the anti apoptotic protein A20. Endocrinology 2002;143:4809-4819.
84. Van Etten E and Mathieu C: Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. Journal Steroides Biochemistry Molecular Biology 2005; 97:93-101.
85. Pittas AG, Lau J, Hu FB and Dawson-Hughes B: Review- The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. Journal Clinical Endocrinology Metabolism 2007; 92:2017-2029.
86. Mokdad AH, Bowman BA, Ford ES, Vinicoor F, Marks JS and Koplan JP: The continuing epidemics of

obesity and diabetes in the United States. Journal American Medical Association 2001; 286:1195-1200.
87. Liu S, Song Y, Ford ES, Manson JE, Buring JE and Ridker PM: Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care 2005; 28:2926-2932.
88. Hypponen E and Power C: Vitamin D status and glucose homeostasis in the 1958 British birth cohort. The role of obesity. Diabetes Care 2006; 29:2244-2246.
89. Fliser D, Stefanski A, Franek E, Fode P, Gudarzi A and Ritz E: No effect of calcitriol on insulin-mediated glucose uptake in healthy subjects. European Journal Clinical Investigation 1997; 27:629-633.
90. Inomata S, Kadowaki S, Yamatani T, Fukase M and Fujita T: Effect of 1 alpha (OH)-vitamin D3 on insulin secretion in diabetes mellitus. Bone Mineral 1986; 1:187-192.
91. Ljunghall S, Lind L, Lithell H, Skarfors E, Selinus I, Sorensen OH and Wide L: Treatment with one-alpha-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance--a prospective randomized double-blind study. Acta Medica Scandnavia 1987; 222:361-367.
92. Orwoll E, Riddle M and Prince M: Effects of vitamin D on insulin and glucagon secretion in non-insulin-dependent diabetes mellitus. American Journal Clinical Nutrition 1994; 59:1083-1087.
93. Nilas L and Christiansen C: Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. Intentional Journal Obesity 1984;8:407-411.
94. Pittas AG, Harris SS, Stark PC and Dawson-Hughes B: The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non diabetic adults. Diabetes Care 2007; 30:980-986.
95. Colak E, Majkic-Singh N, Stankovic S, Sreckovic-Dimitrijevic V, Djordjevic PB, Lalic K and Lalic N: Parameters of antioxidative defence in type 2 diabetic patients with cardiovascular complications. Annals Medicine 2005; 37:613–620.
96. Da Costa, LA, García-Bailo B, Badawi A, and El-Sohemy A: Genetic determinants of dietary antioxidant status. In Bouchard C. and Ordovas JM [eds.]. Recent Advances in Nutrigenetics and Nutrigenomics Elsevier, New York, NY 2012, in press.
97. Han SN, Adolfsson O, Lee CK, Prolla TA, Ordovas J and Meydani SN: Vitamin E and gene expression in immune cells. Annals NY Academy Science. 2004; 1031:96–101.
98. Adolfsson O, Huber BT and Meydani SN: Vitamin E-enhanced IL-2 production in old mice: naive but not memory T cells show increased cell division cycling and IL-2 –producing capacity. Journal Immunology 2001; 167:3809–3817.
99. Singh U and Jialal I: Anti-inflammatory effects of α-tocopherol. Annals NY Academy Science 2004; 1031:195–203.
100. Garcia-Bailo B, El-Sohemy A, Haddad P, Arora P, BenZaied F, Karmali M and Badawi A: Vitamins D, C and E in the prevention of type II diabetes mellitus. Modulation of inflammation and oxidative stress. Biologics 2011;5:7-19.
101. Pittas AG, Lau J, Hu FB and Dawson-Hughes B: Review- The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. Journal Clinical Endocrinology Metabolism 2007; 92:2017-2029.

How to cite this article:
Gupta VK, Pathak A, Gahlot M, Verma RC and Singh CV: Impact of Vitamins in prevention of risk factors associated with Type-2 Diabetes mellitus. *Int J Pharm Sci Res* 2013; 4(4); 1335-1347.