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DIETARY SUPPLEMENTS: BUILDS BODY STRUCTURE BUT ALSO BREAKS

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ABSTRACT:

Dietary supplement can be defined as any vitamin, mineral, amino acids, added chemical substances, animal derived or herbal products that is added to the diet to improve human health. Scientists and health professionals agree that dietary supplements can be under certain conditions beneficial to human health, but should not replace complete and balanced daily meals of foods which are necessary for a healthful diet. The most authoritative national agency U.S. Food and Drug Administration (FDA) emphasized that "…unlike drugs, dietary supplements are not intended to treat, diagnose, prevent, or cure diseases. Dietary supplements should not make claims, such as "reduces pain" or "treats heart disease", etc.…". Globally, dietary supplement market stood at over US$90 billion in 2013, and on top is the US market with over 30 billion every year. For many years informed medical sources like doctors, nurses, pharmacists, nutritionists and medical authorities agree that there's a lot of wrong information in the supplements market. Many dietary supplements, even in the USA that has some of the most experienced health agencies, managed to escape the safety tests, labeling and health regulations. From 2007, some of the most well-known scientists in the USA on nutrition, metabolism and epidemiology reviewed the evidence on multivitamin/mineral supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Randomized Control Trials of dietary supplements increased substantially in the last decade in many developed countries. The results are mixed but the majority is negative for health benefits or for preventing diseases. In 2013 three papers and an overall review of the results for the last decade with the title "Enough is enough. Stop wasting money on vitamin and mineral supplements" was published in the prestigious medical journal Annals of Internal Medicine in the USA. The influence of these research results was spread to other developed countries and more critical appraisals were published on dietary supplements. This review article covers the most important aspects of dietary supplements, the trends in global market, the national and international regulations of various products. Also, examines the debate and arguments of health professionals. The review examines in a systematic way the most important studies that were published in the scientific literature in the last few years on the most widespread dietary supplements and their results on benefits or risk to human health. It covers dietary supplements taken by young, elderly, pregnant women, athletes and people with deficiencies which were self-prescribed and on the international market.

KEYWORDS:

DIETARY SUPPLEMENTS, BALANCER DIET, VITAMINS, MINERALS, RANDOMIZED CONTROL TRIALS, HEALTH BENEFIT, RISK, GLOBAL DIETARY SUPPLEMENTS MARKET.

DIETARY SUPPLEMENTS:

Overview-From the beginning of human civilization diet was mostly plant foods that could be easily gathered and sea foods. Hunter-gatherers later contributed meat products by big game. This was the diet of most humans until about 10,000 BC, at which time the development of agriculture and animal husbandry provided more meat and grains for the whole family. Nobody knew about vitamins, minerals, proteins, carbohydrates and fats and their role in human nutrition. The various people in the continents of the Earth developed nutritious local cuisines with mostly local products that sustained their health, whereas by trial and error choose a variety of foods and cooking methods that lead to physical strength, health, and fertility. The common wisdom of native cultures knew which foods and herbs had special properties for energy, nutrition and extra health benefits for children, pregnant women and elders. Everyday diets were "supplemented" to make up for deficiencies as far back as native cultures. Native Americans, for example, knew to drink a tea made from pine bark and needles for scurvy containing high concentration of ascorbic acid, which was later found by science to be a vitamin C deficiency disease.

BALANCED DIET AND DIETARY SUPPLEMENTS:-

Dietary supplement can be defined as any vitamin, mineral, added chemical substance, herbal product, botanicals, amino acids, or other ingestible preparation that is added to the diet to benefit human health. Dietary supplements are used worldwide and represent a broad category of ingestible products that are distinguishable from conventional foods and drugs. 1-5 All developed countries have special legislation concerning dietary supplement (for example, U.S. Dietary Supplement Health and Education Act, 1994). In countries, such as Australia and Canada, dietary supplements and drugs are regulated similarly, and only ingredients deemed acceptable by the Therapeutic Goods Administration of Australia or the Natural Health Products Directorate of Canada can be sold as dietary supplements.

A fundamental question that everybody asks these days that most people are very aware that nutrition plays a very important role in health is, if conventional, balanced and without supplements diet can cover all the needs of the human body for a healthy lifestyle until old age. Nutritionists and health professionals argued for years that people can get the most important food requirements that their body needs each day from a conventional, balanced and regular daily diet. Today's dietary guidelines from health and nutrition agencies cover more than 40 nutrients that are subdivided into 6 categories: carbohydrates, fats, proteins, vitamins, minerals and water. Daily nutrient recommendations are collectively known as dietary reference intakes (DRIs). A healthy diet is one that favours "real" fresh whole foods that have been sustaining people throughout the millenniums. Whole foods supply the needed vitamins, minerals, protein, carbohydrates, fats, and fiber that are essential to good health. In contrast, commercially prepared and fast foods are often lacking nutrients and contain inordinate amounts of sugar, salt, saturated and trans-fats, all of which are associated with the development of diseases. A balanced diet is a mix of food from the different food groups (vegetables, legumes, fruits, grains, protein foods, meat, and dairy). Variety involves eating different foods from all the food groups that helps to ensure that you receive all the nutrients necessary for a healthy diet. The components of the Mediterranean diet have been evaluated as substantially beneficial to human health.

The World Health Organization (WHO) makes the following recommendations for a balanced and healthy diet: a. eat roughly the same amount of calories that your body is using, b. a healthy weight is a balance between energy consumed and energy that is 'burnt off', c. limit intake of fats, and prefer unsaturated, than saturated fats and trans fats, d. increase consumption of plant foods, particularly fruits, vegetables, legumes, whole grains and nuts, e. limit the intake of sugar, salt/sodium consumption from all sources and ensure that salt is iodized, f. eat a diet with essential micronutrients such as vitamins and certain minerals.16,17

CONCERN AMONG HEALTH PROFESSIONALS FOR THE EXCESSIVE USE OF DIETARY SUPPLEMENTS:

In the last decade national medical authorities, health professionals and nutritionists in developed countries became aware of the widespread and rapid increase of dietary supplements (DS) and excessive consumption by a wide range of the population. The global market is flooded with a variety of dietary supplements that have false therapeutic claims (difficult to test experimentally) and products which can be imported and distributed through the internet advertisements. Like drugs, dietary supplements have risks and side effects. But sellers aren't required to do research studies in people to prove that dietary supplements are safe. And unlike drugs, DS are mostly self-prescribed with no input from informed medical sources like doctors, nurses, or pharmacists. Medical authorities agree that there's a lot of wrong information in the supplements market. Even for those who are usually well informed, it can be hard to find reliable information about the safe use and potential risks of DS. 46-48 The most commonly reported reasons for using supplements were to "improve" or "maintain" overall health. Women used calcium products for "bone health" or for improving healthy skin appearance, whereas men were more likely to report supplement use for "heart health or to "lower cholesterol". Young people use supplements to enhance body function in sports. Older adults report motivations related to heart, bone and joint, and eye health. The consumption of DS is excessive in the USA with most Americans taking multivitamins. The primary reasons given for supplement use are for overall health and wellness or to fill nutrient gaps.49,50 The concern of health professionals is that very little is known about the efficacy of DS for disease prevention and health needs. American scientists emphasize that randomized clinical trials are difficult because they tend to be short in duration, whereas many of the chronic diseases of public health concern have a long latency period (i.e., allergies, cancer, and cardiovascular disease). Also, more investigations on the complex interplay of social, psychological, and economic determinants that motivate supplement choices are needed. At the same time the US FDA tracks reports of illness, injury, or reactions from dietary supplements. Recent FDA information of adverse or side effects shows that the number of reports has continued to climb each calendar year: 2010: 1,009 reports of DS for adverse health events to consumers, 2011: 2,047 reports and 2012: 2,844 reports. Exposures to supplements accounted for more than 100,000 calls to US poison control centers in 2013. Of these calls, more than

8,000 people were reportedly treated in health care facilities and 2 deaths reported to poison control centers.51 Emergency health departments in the USA between 2004-2013 received 23.000 emergency visits per year attributed to adverse health events related to DS consumption, with 2,154 cases needing hospitalization.52 Also, from 2012 to 2014 the FDA received 114 reports of adverse events (hepatitis outbreak, liver damage) involving consumers who ingested OxyELITEPro (promotes weight loss) supplements.53 From 2007, some of the most well known scientists in the USA on nutrition, metabolism and epidemiology (professors Stampfer, Willett , Harvard, School of Public Health, and Bruce Ames and Joyce McCann, Nutrition and Metabolism Center, Children's Hospital Oakland Research Center) following a National Institutes of Health, reviewed the evidence on multivitamin/mineral (MVM) supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Their bottom line was: "…… everyone would agree that all persons. should be encouraged to eat a good diet, but we are far from achieving this goal, especially among the poor. In most cases, a simple way to improve micronutrient status is to take an MVM. However, even if one eats an ideal diet and takes an MVM, some vitamins can remain below recommended concentrations in some groups...". "…The panel excluded this highly relevant body of evidence from consideration, and it came to the conclusion, "….The present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease". We contend that, by conveying the impression that long-term Randomized Controlled Trials (RCTs), which are inherently limited, represent the only scientific evidence relevant to "evidence-based decision making," the panel presents a highly biased and misleading picture...". 54 Many dietary supplements, even in the USA that has some of the most experienced health agencies, managed to escape the safety tests, labeling and regulations. The American agencies every year find toxic DS products in the US market that were finally recalled because they were found to contain banned toxic substances. Between 2009 and 2012, the FDA recalled 274 dietary supplements. The analysis of these DS was performed by GC-MS and found to contain toxic substances or additional pharmaceutical adulterants which were banned. 55,56

SCIENTIFIC PAPERS ON THE ROLE OF VITAMIN AND MINERAL SUPPLEMENTS:-

In the last decade the Randomized Control Trials (RCTs) of dietary supplements increased substantially in many developed countries. The results are mixed but the majority was negative for DS promoting health or preventing diseases. In 2013 three papers and an overall review of the results for the last decade on DS with the title "Enough is enough. Stop wasting money on vitamin and mineral supplements" were published in the prestigious and influential medical journal Annals of Internal Medicine in the USA. In the first paper scientists reviewed in a systematic way all trial evidence (carried by the U.S. Preventive Services Task Force) for the recommendation on the efficacy of vitamin supplements for primary prevention for adults with no nutritional deficiencies. The review contained 3 trials of multivitamin supplements and 24 trials of single or paired vitamins that randomly assigned to more than 400,000 participants, the authors concluded that there was no clear evidence of a beneficial effect of supplements on all-cause mortality, cardiovascular disease, or cancer.57 In the second paper, researchers evaluated the efficacy of a daily multivitamin to prevent cognitive decline among 5,947 men aged 65 years or older participating in the Physicians' Health Study II. After 12 years of follow-up, there were no differences between the multivitamin and placebo groups in overall cognitive performance or verbal memory.58 These findings were compatible with a recent review of 12 fair-to good-quality trials that evaluated dietary supplements, including multivitamins, B vitamins, vitamins E and C, and omega-3 fatty acids, in persons with mild cognitive impairment or mild to moderate dementia. None of the supplements improved cognitive function.59 In the third paper, Lamas and associates60 , assessed the potential benefits of a high-dose, 28- component multivitamin supplement in 1,708 men and women with a previous myocardial infarction participating in TACT (Trial to Assess Chelation Therapy). After a median follow-up of 4.6 years, there was no significant difference in recurrent cardiovascular events with multivitamins compared with placebo (hazard ratio, 0.89). 60 The supporting editorial in the same journal, 61 added some previous highly relevant research papers, reviews and guidelines that have appraised the role of vitamin and mineral supplements in primary or secondary prevention of chronic disease but have consistently found null results or possible harms. 62,63 Evidence involving tens of thousands of people randomly assigned in many clinical trials shows that β-carotene, vitamin E, and possibly high doses of vitamin A supplements increase mortality and that other antioxidants, folic acid and B vitamins, and multivitamin supplements have no clear health benefit.62,64-66 Despite sobering evidence of no benefit or possible harm, use of multivitamin supplements increased among U.S. adults in the last decade (reaching over 30 billion in 2013). Similar trends have been observed in the United Kingdom and in other European countries.67 The editorial concludes "…the message is simple conclude the scientists: Most supplements do not prevent chronic disease or death, their use is not justified, and they should be avoided…".

ARGUMENTS IN SUPPORT OF DIETARY SUPPLEMENTS AND HEALTH BENEFITS:-

After the publication of the scientific papers in Annals of Internal Medicine and the editorial "Enough Is enough: Stop wasting money on vitamin and mineral supplements" (2013) scientists of Oregon State University, Linus Pauling Institute (December 2013), an institute specializing on nutrition benefits of DS, carried a supporting note in their website for the balanced diet and prudent use of DS to fill

the gap of useful micronutrients, vitamins and minerals for humans. Under the title "The case is far from closed for vitamins and mineral supplements". 68 "… While a well-balanced diet is the best way to get all of one's essential nutrients, the reality is that Americans don't get enough of them trough diet alone. From the National Health and Nutrition Examination Survey (NHANES) we know that the large majority of the US population is not "wellnourished" and falls short of getting all of their vitamins and minerals from their diet in levels recommended." . "… Studies have shown that people who take multivitamin/mineral (MVM) supplement with the recommended doses of the most vitamins and minerals can fill most of these nutritional gaps safety and at very low cost.69,70,71 Contrary to the impression that the authors (of the paper "enough is enough…") give in their editorial, the US population is inadequate in many vitamins and minerals, a result of the energy dense and nutrient-poor dietary pattern of Western populations, rather than overconsuming MVM and other DS. The known biological functions of vitamins and nutritionally-essential minerals are to maintain normal cell function, metabolism, growth and development, through their roles as essential cofactors in hundred of enzyme reactions and other biological processes-not to prevent or treat chronic disease. Nevertheless, the largest and longest randomized controlled trial (RCT) of MVM supplements conducted to date, the Physicians' Health Study II (PHS II), found a significant 8% reduction in total and epithelial cell cancer incidence in male physicians, and a 12% reduction in total cancer incidence excluding prostate cancer. The PHS II also found a significant 9% reduction in the incidence of total cataract. The findings are consistent with those of several other RCTs, and are even more impressive given the fact that the conventional RCT design is strongly biased against showing benefits of essential nutrients, in contrast to pharmaceutical drugs.72-77 Finally, the scientists of Linus Pauling Institute concluded "… Therefore, taking a daily MVM supplement will not only help fill the known nutritional gaps in the average American diet, thereby assuming normal biological function and metabolism and supporting good health, but may also have the added benefit of reducing cancer and cataract risk-which no existing pharmaceutical drug can do. To call "the case…closed" and label MVM supplements as useless, harmful or wasteful is highly premature and unscientific, and does not serve public health". In the last few years numerous books and collections of scientific results were published or projected on websites of health agencies on dietary supplements, safety, cost, efficacy and health benefits vs risks.78-80

RECENT SCIENTIFIC STUDIES ON VITAMIN AND MULTIVITAMIN SUPPLEMENTS:-

Vitamin and multivitamin supplements in combination with calcium and antioxidants are the most widespread dietary supplements used by elderly people, pregnant women and people with disabilities for improving health, perinatal depression, improvement for neurologic and cognitive function, osteoporosis and progression of cancer.

However, clinical trials on the use of vitamin supplements for promotion of health and prevention of disease have failed to demonstrate the strong associations seen in observational studies. In Western countries (US and W. Europe) it is fairly common the consumption of multivitamins among the elderly to prevent disease and improve health. In the US half of adults report using one or more DS. Although epidemiologic evidence suggests that a diet rich in fruits and vegetables does have a protective effect on health, clinical trials on the use of vitamin supplements have failed to demonstrate their health or protective benefits. 81 Other scientific data summarized in a recent review (29 clinical trials involving 24,300 women) do not support that routine vitamin C supplementation alone or in combination with other supplements for the prevention of fetal or neonatal death, poor fetal growth, preterm birth or pre-eclampsia. Additionally, further research is required to elucidate the possible role of vitamin C in the prevention of placental abruption and prolabor rupture of membranes.82 A recent review examined 35 studies on diet, essential nutrients, and DS and their role in perinatal depression. The studies were grouped into four main categories based on the analysis of dietary intake: adherence to dietary patterns (9 studies); full panel of essential nutrients (6 studies); specific nutrients (including B vitamins, Vitamin D, calcium and zinc; 8 studies); and intake of fish PUFAs (12 studies). While 13 studies found no evidence of an association, 22 studies showed protective effects from healthy dietary patterns, multivitamin supplementation, fish and PUFA intake, calcium, Vitamin D, zinc and possibly selenium. Given the methodological limitations of existing studies and inconsistencies in findings across studies, the evidence on whether nutritional factors influence the risk of perinatal depression is still inconclusive.83 Another randomized controlled trial (RCT) investigated the B-12 supplementation benefits on neurologic and cognitive function in moderately vitamin B-12-deficient people. Results of the RCT study did not support the hypothesis that the correction of moderate vitamin B-12 deficiency, in the absence of anemia and of neurologic and cognitive signs or symptoms, has beneficial effects on neurologic or cognitive function in later life.84 Supplementation of vitamin B (folate, B6 and B12) has been investigated by a meta-analysis of 4 RCTs, for prevention or reduction in osteoporotic fracture and bone turnover. The results of this analysis failed to identify a risk-reducing effect of daily supplementation of B vitamins on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy (a blood test used to detect levels of homocysteine). In addition, the study did not find any positive effects of B vitamin supplementation on bone turnover.85 Older adults in most countries use vitamin supplements (vitamins A, B, C, D and E) on the promise for health improvements and prevention of degenerative diseases (mortality, cancer, cardiovascular and cerebrovascular diseases, cataracts, age-related macular degeneration and bone diseases). The results of the most

important studies on vitamins were summarized in a recent review. Data from studies demonstrate considerable variations, most confirming little to no benefit following supplementation in healthy adults. However, clear roles exist for vitamin supplementation in states of deficiency and in subgroups of older adults at high risk for deficiency of specific or multiple vitamins.86

Vitamin E supplementation and other vitamins have been advocated for positive benefits in pregnancy. A review collected 21 RCTs, involving 22,129 women, which assessed vitamin E in combination with vitamin C and/or other antioxidant agents. The data from these studies did not support routine vitamin E supplementation in combination with other supplements for the prevention of stillbirth, neonatal death, preterm birth, pre-eclampsia, preterm or term PROM or poor fetal growth.90

PROTEIN/AMINO ACID SUPPLEMENT RISKS:-

Protein is an essential macronutrient needed by the human body for growth and maintenance. Foods rich in animal protein are meat, fish, eggs, poultry, and dairy products, while plant foods high in protein are mainly legumes, nuts, and grains. The current recommended dietary allowance (RDA) for protein is 0.8 g protein/kg body weight/day for adults (for children 1.5 g protein/kg body weight/day, and for adolescents 1.0 g protein/kg body weight/day) [1]. However, high protein diets (defined as an intake above the current RDA) are promoted intensively by the nutritional supplements industry and they are considered to be "the gold standard" by many athletes (especially bodybuilders) for muscle development and/or body fat loss. On the other hand, several scientists claim that the overuse of protein supplements or high dietary protein intake could cause disorders to human health [127-134].

Diet which is high in protein generates a large amount of acid in body fluids [128]. The kidneys respond to this dietary acid challenge with net acid excretion, and, concurrently, the skeleton supplies buffer by active resorption of bone resulting in excessive calcium loss [128]. Moreover, acid loading directly inhibits renal calcium reabsorption leading to hypercalciuria in combination with the exorbitant bone loss [130-131]. In a metabolic study an increase in protein intake from about 47 to 112 g caused an increase in urinary calcium and a decrease in calcium retention. The data indicated that protein-induced hypercalciuria was due to an elevation in glomerular filtration rate and a lower fractional renal tubular reabsorption of calcium, the latter of which caused by the increased acid load on the renal tubular cells [135]. Another study on subjects consuming diets containing 48 g protein daily to 142 g showed that urinary calcium doubled, while the calcium balance became negative [136]. In this study the subjects were on a well-balanced diet for 2 weeks which was followed by 4 days of an experimental diet containing one of three levels of protein (low, medium, or high). Urinary calcium excretion was significantly higher, and urinary N-telopeptide excretion (indicator of bone resorption) was significantly greater during the high protein than during the low protein intake. Data suggested that, at high levels of dietary protein, at least a portion of the increase in urinary calcium reflected increased bone resorption [137]. Additionally, subjects on a low-carbohydrate high-protein (LCHP) diet for 6 weeks had increased urinary calcium levels, decreased calcium balance, and decreased serum osteocalcin concentrations [133]. In a prospective study, protein was associated with an increased risk of forearm fracture for women who consumed more than 95 g per day compared with those who consumed less than 68 g per day.

Low fluid intake and excessive intake of protein are important risk factors for kidney stones [130]. Protein ingestion increases renal acid excretion, and acid loads, in turn, may be buffered in part by bone, which releases calcium to be excreted by the kidney. This protein-induced hypercalciuria could lead to the formation of calcium kidney stones [131] . Excessive intake of animal protein is therefore associated with hyperuricosuria, a condition present in some uric acid stone formers [132]. Uric acid solubility is largely determined by the urinary pH. As the pH falls below 5.5 to 6.0, the solubility of uric acid decreases, and uric acid precipitates, even if hyperuricosuria is not present.

Moreover, high protein diet could cause disorders of liver function and precipitated progression of coronary artery disease. Hyperalbuminemia and elevated transaminases have been associated with high-protein diet [134]. Individuals on high protein supplements developed intermittent abdominal pain, transient elevations in transaminases, and hyperalbuminemia without there being any identifiable cause. The symptoms and abnormalities on the laboratory tests resolved after the high protein intake was discontinued. In a case-control study, subjects (treatment group/TG) were studied for 1 year by using myocardial perfusion imaging (MPI), echocardiography (ECHO), and serial blood work [132]. MPI and ECHO were performed at the beginning and end of the study for each individual. The TG group studied modified their dietary intake as instructed. Additional subjects (high protein group/HPG) elected a different dietary regimen consisting of a "high-protein" diet . Subjects in the TG demonstrated a reduction in each of the independent variables studied with regression in both the extent and severity of coronary artery disease (CAD) as quantitatively measured by MPI. Individuals in the HPG showed worsening of their independent variables. These results would suggest that high-protein diets may precipitate progression of CAD through increases in lipid deposition and inflammatory and coagulation pathways [129].

CALCIUM/VITAMIN D SUPPLEMENT RISKS:-

Calcium (Ca) is an essential element in the human diet, but there is continuing controversy regarding its optimal intake, and its role in the pathogenesis of cardiovascular diseases, osteoporosis and bone fractures. Most studies show little evidence of a relationship between calcium intake and bone density, or the rate of bone loss. Very few

food contain vitamin D. Synthesis of vitamin D occurs in the skin, after exposure to sun light (especially UV-B radiation), is the major natural source in humans.91 Vitamin D refers to a group of fat-soluble secosteroid compounds responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol). A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalacia (or rickets in children). Dietary supplements containing Ca and vitamin D are widespread but there is a controversy regarding their optimal intake and their role in osteoporosis.92

A scientific meta-analysis investigated data from 9 trials in order to provide a quantitative assessment of the efficiency of intermittent, high dose vitamin D treatment on falls, fractures, and mortality among older adults. The high dose, intermittent vitamin D therapy did not decrease all-cause mortality among older adults. No benefit was seen in fracture or fall prevention. The risk ratio for hip fractures was 1.17 (95% Confidence Interval), while for non-vertebral fractures it was 1.06 and the risk ratio for falls was 1.02. All these results showed very small beneficial effects. Scientists concluded that supplementation of intermittent, high dose vitamin D may not be effective in preventing overall mortality, fractures, or falls among older adults. 95

The Women's Health Initiative for Calcium and vitamin D supplementation Study, was a 7 year, randomized, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36, 282 community dwelling postmenopausal women. The study followed the Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data. In metaanalyses of placebo controlled trials of Ca or Ca and vitamin D data were available for 28, 072 participants from 8 trials. In total 1,384 individuals had an incident myocardial infarction or stroke. Ca or combination of Ca and vitamin D increased the risk of myocardial infarction (relative risk 1.24) and the composite of myocardial infarction or stroke (1.15). Scientists concluded that Ca supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction.96

BALANCED DIET AND DIETARY SUPPLEMENTS OF OMEGA-3 FATTY ACIDS:-

Omega-3 and omega-6 fatty acids (σ-3 & -6 FAs) are polyunsaturated fatty acids (PUFAs) considered to be important in human physiology. The most widely available dietary source of omega-3 FAs is oily fish, such as salmon, herring, mackerel, anchovies, menhaden, and sardines. Omega FAs have significant influence on the ratio and rate of production of eicosanoids, a group of hormones intimately involved in the body's inflammatory and homeostatic processes, which include the prostaglandins, leukotrienes, and thromboxanes. A recent trend has been to fortify food with omega-3 FAs supplements, such fortified bread, pizza, yogurt, orange juice, children's pasta, milk, eggs, confections, and infant formula to reduce mainly the risk for CVDs. A review investigated a series of 11 studies for the association of dietary supplements of omega3 fatty and risk to cardiovascular deaths with a total of 39,044 patients (after myocardial infarction, heart failure, peripheral vascular disease, etc) The average dose of EPA/DHA (fish oil containing EicosaPentaenoic Acid/ DocosaHexaenoic Acid) was 1.8 g/day and the mean duration of follow-up was 2.2 years. Dietary supplementation with omega-3 fatty acids significantly reduced the risk of cardiovascular deaths at 0.87, sudden cardiac death 0.87, all-cause mortality 0.92, and nonfatal cardiovascular events 0.92. The mortality benefit was largely due to the studies which enrolled high risk patients. Meta-regression failed to demonstrate a relationship between the daily dose of omega-3 fatty acid and clinical outcome. The scientists concluded that dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events. 97 A systematic review explored more than 15,000 articles in the scientific literature, including 48 randomized control trials (with 36,913 participants) and 41 epidemiological cohort studies that focused on health benefits and risks from diets with additional omega-3 (σ-3) fatty acids. The health effects were concerned with cardiovascular diseases, general mortality and malignant neoplasms. The pooled estimate showed no strong evidence of reduced risk of total mortality (relative risk 0.87) or combined cardiovascular events (0.95) in participants taking additional omega-3 fatty acids. Scientists concluded that long chain and shorter chain omega-3 fatty acids do not have a clear effect on total mortality, combined cardiovascular events, or cancer.98

Many studies in the last decade showed that long-chain omega-3 polyunsaturated fatty acids (PUFAs) or omega-3 PUFAs are able to modulate inflammation, hyperlipidemia, platelet aggregation, and hypertension, under different mechanisms for conditioning cell membrane function and composition eicosanoid production, and gene expression. A review in 2014 analyzed the influence of omega-3 PUFAs status and intake on brain function, cardiovascular system, immune function, muscle performance and bone health in older adults. It was found that omega-3 fatty acids can have benefits in reducing the risk of cognitive decline in older people, but more studies are needed to confirm the role of omega-3 (σ-3) in maintaining bone health and preventing the loss of muscle mass and function associated with ageing.99

Observational and randomized controlled trials (RCTs) have produced enough data to suggest that higher fatty fish intake is strongly is linked with reduced risk of fragility fracture. Human studies largely support that a greater intake of total PUFAs, total n-6 (σ-6 FAs) fatty acid, and total n-3 (σ-3) fatty acid, contributed for higher bone mineral density and reduced risk of fragility fracture.100

Also, omega fatty acids in combination with other antioxidants, such as resveratrol, can have a major therapeutic role. A recent review collected some of the key studies involving the health benefits supported by a combination of resveratrol and σ-3 FAs intake. Many studies showed that resveratrol, as a potent antioxidant reduces oxidative stress in endoplasmic reticulum, and proved to have a significantly protective role in most important pathophysiological factors associated with CVD conditions.

Currently, there is increasing evidence of the benefits of omega-3 by different medical professional bodies with the stronger evidence for cardiovascular disease (CVDs). There is a broad consensus among scientists that fish and seafood are the optimal sources of n-3 FAs and consumption of approximately 2-3 servings per week is recommended for good health. But it has been noted that the scientific evidence of benefits from n-3 FAs supplementation has diminished over time, probably due to a general increase in seafood consumption in developed countries, better pharmacological intervention and acute treatment of patients with CVD diseases.102-104

DIETARY ZINC, IRON AND SELENIUM SUPPLEMENTATION, HEALTH BENEFITS/RISKS:-

Zinc is essential trace element for normal biological growth, reproduction and immune function. In addition, Zn is vital for the functionality of more than 300 enzymes, for the stabilization of DNA, and for gene expression. Zinc deficiency is estimated to be responsible for 4% of global child morbidity and mortality. The adult human contains 2–3 g of zinc (Zn). Conservative estimates suggest that around 25% of the world's population is at risk of zinc deficiency.105 Most of the affected are poor, and rarely consume foods rich in highly bioavailable zinc, while subsisting on foods that are rich in inhibitors of zinc absorption and/or contain relatively small amounts of bioavailable zinc. Food choice is a major factor affecting risk of zinc deficiency. A major challenge that has not been resolved for maximum health benefit is the proximity of the recommended dietary allowance (RDA) and the reference dose (RfD) for safe intake of zinc. The current assumed range between safe and unsafe intakes of zinc is relatively narrow.106

A recent review included data from 21 randomized controlled trials (RCTs) reported in 54 papers involving over 17,000 women and their babies. The results showed that there was a 14% relative reduction in preterm birth for zinc compared with placebo. These results appeared in primarily in trials involving women of low income and this has some relevance in areas of high perinatal mortality. There was no convincing evidence that Zn supplementation during pregnancy resulted in other useful and important health benefits. According to the scientists these results reflected poor nutrition in impoverished areas and the need for a balanced diet than dietary Zn supplements.107 Scientists experimented with Zinc supplementation that may remodel the immune alterations in elderly leading to healthy ageing. Several zinc trials have been carried out with contradictory data, perhaps due to incorrect choice of an effective zinc supplementation in old subjects showing subsequent zinc toxic effects on immunity. Old subjects with specific IL-6 polymorphism were more prone for zinc supplementation than the entire old population, in whom correct dietary habits with foods containing zinc (Mediterranean diet) may be sufficient in restoring zinc deficiency and impaired immune response.

It is well known that Zinc (Zn) and Iron (Fe) are essential minerals often present in similar food sources. A review analyzed the current medical and nutritional literature on Zn and Fe supplementation and its impact on mood or cognition in pre-menopausal women. 10 RCTs and one non-randomized controlled trial were found to meet the inclusion criteria. The results showed that 7 studies found improvements in aspects of mood and cognition after iron supplementation. Iron supplementation appeared to improve memory and intellectual ability in participants aged between 12 and 55 years of age regardless of whether the participant was initially iron insufficient or iron-deficient with anemia. Also, 3 RTCs provided evidence to suggest a role for Zn supplementation as a treatment for depressive symptoms. Overall, the current scientific literature indicated a positive effect of improving Zn status on enhanced cognitive and emotional functioning. However, further study involving well-designed randomized controlled trials is needed to identify the impact of improving iron and zinc status on mood and cognition.109

ron deficiency anemia in humans is an important public health issue, especially for infants, children, and women with menorrhagia. Oral iron supplements are the cheapest, safest, and most effective treatment. A retrospective study collected for two years 41 patients with iron deficiency anemia who continuously took oral ferric for over one month and then switched to oral ferrous due to poor therapeutic effects. The results showed that the mean blood test values for all patients significantly increased after switching to ferrous iron. This study found that blood test values improved after iron deficiency anemia female patients who displayed poor therapeutic effects with oral ferric switched to ferrous. A literature review in the same study showed that the risk for gastrointestinal problems with ferrous is higher than that with ferric.113

Randomised Control Trials or quasi-randomised trials evaluating the effects of oral preventive supplementation with daily iron, iron + folic acid or iron + other vitamins and minerals during pregnancy.

The study concluded that iron supplementation reduces the risk of maternal anaemia and iron deficiency in pregnancy but the positive effect on other maternal and infant outcomes is less clear. Implementation of iron supplementation recommendations may produce heterogeneous results depending on the populations' background risk for low birthweight and anaemia, as well as the level of adherence to the intervention. 114 Recent

studies showed that intermittent iron supplementation is a promising strategy in reducing iron deficiency and iron deficiency anaemia. Also, a small number of studies investigated the effect of iron interventions on developmental outcomes, such as growth and cognition, and provided mixed results. Some studies reported that iron intervention increased morbidity and caused unfavourable shifts in the gut microbial composition along with increases in intestinal inflammation, particularly in children with a high infectious disease burden. Scientists suggested that that there is a need for studies in children from low and middle-income populations to provide evidence for the beneficial effects of iron interventions on functional outcomes (iron deficiency and anaemia), and to explore potential mechanisms underlying the negative effects of iron reported in recent trials.115

Selenium is another very important trace element (micronutrient) incorporated into selenoproteins that have a wide range of pleiotropic effects, ranging from antioxidant and anti-inflammatory effects to the production of active thyroid hormone. In the past 10 years, the discovery of disease-associated polymorphisms in selenoprotein genes has drawn attention to the relevance of selenoproteins to health. Low selenium status has been associated with increased risk of mortality, poor immune function, and cognitive decline. Higher selenium status or selenium supplementation has antiviral effects, is essential for successful male and female reproduction, and reduces the risk of autoimmune thyroid disease. Prospective studies have generally shown some benefit of higher selenium status on the risk of prostate, lung, colorectal, and bladder cancers, but findings from trials have been mixed, which probably emphasises the fact that supplementation will confer benefit only if intake of a nutrient is inadequate. Supplementation of people who already have adequate intake with additional selenium might increase their risk of type-2 diabetes. The crucial factor that needs to be emphasised with regard to the health effects of selenium is the inextricable U-shaped link with status; whereas additional selenium intake may benefit people with low status, those with adequate-to-high status might be affected adversely and should not take selenium supplements.111

Selenium supplementation and cancer has been investigated by various epidemiological studies. A recent extensive review analysed data from 55 prospective observational studies (including more than 1,100,000 participants) and 8 RCTs (with a total of 44,743 participants). Although an inverse association between selenium exposure and the risk of some types of cancer was found in some observational studies, this cannot be taken as evidence of a causal relation, and these results should be interpreted with caution. These studies have many limitations, including issues with assessment of exposure to selenium and to its various chemical forms, heterogeneity, confounding and other biases. Conflicting results including inverse, null and direct associations have been reported for some cancer types. RCT studies have yielded inconsistent results, although the most recent studies, characterized by a low risk of bias, found no beneficial effect on cancer risk, more specifically on risk of prostate cancer.

DIETARY PHYTOCHEMICALS, HERBS, LOSS OF WEIGHT AND SUPPLEMENTS:-

The global market of Dietary Supplements (DS) is full of numerous “natural” therapies with incredulous claims and very little evidence of health benefits. Dietary supplements involving flavonoids, polyphenols, herbal therapies (Ginkgo, ginseng, Echinacea, etc), and for reduction of body weight (chitosan, picolinate, Ephedra sinica, Garcinia cambogia, etc) are claiming beneficial biological effects without risk of adverse effects. But the scientific evidence is very different.

Numerous studies have shown that although consumption of dietary phytochemicals such as flavonoids has been suggested to have beneficial biological effects including the prevention of cancer and heart disease, there is considerable evidence to suggest that such compounds are not without risk of adverse effects. The risk of adverse effects is likely increased by the use of pharmacological doses in prevention/treatment and supplement situations and genetic polymorphisms or drug-drug interactions that increase the bioavailability of test compounds.116 The DS market is full of popular herbal remedies. Scientific studies investigated the efficacy and safety of ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. The safety assessments were based on systematic reviews of RCTs. Although data supported the efficacy of some of these popular herbal medicinal products, the published evidence suggests that ginkgo is of questionable use for memory loss and tinnitus but has some effect on dementia and intermittent claudication. St. John's wort was efficacious for mild to moderate depression, but serious concerns exist about its interactions with several conventional drugs. Well-conducted clinical trials do not support the efficacy of ginseng to treat any condition. Echinacea may be helpful in the treatment or prevention of upper respiratory tract infections, but trial data are not fully convincing. Saw palmetto has been shown in short-term trials to be efficacious in reducing the symptoms of benign prostatic hyperplasia. Kava is an efficacious short-term treatment for anxiety. Studies showed that none of these herbal medicines were free of adverse effects. Because the evidence is incomplete, risk-benefit assessments are not completely reliable, and much knowledge is still lacking.117

Numerous supplements are used in the global market for body weight reduction without evidence of effective effects and some of them containing risks. An overall critical review assessed the efficacy by using 5 systematic reviews and meta-analyses and 25 additional trials. Data on the following dietary supplements were identified: chitosan, chromium picolinate, Ephedra sinica, Garcinia cambogia, glucomannan, guar gum, hydroxy-methylbutyrate, plantago psyllium, pyruvate, yerba maté, and yohimbe. The

reviewers identified some encouraging data but no evidence beyond a reasonable doubt that any specific DS was effective for reducing body weight. The only exceptions were for E. sinica– and ephedrine-containing supplements, which have been associated with an increased risk of adverse events. Reviewers concluded that the evidence for most DS as aids in reducing body weight was not convincing. None of the reviewed DS can be recommended for over-the-counter use.118

A large study involving124 086 men and women [Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), and Nurses' Health Study II (NHS II)] measured self-reported change in weight over multiple four year time intervals between 1986 and 2011. Results showed that Increased consumption of most flavonoid (flavonols, flavan-3-ols, anthocyanins, flavonoid polymers) was inversely associated with weight change over four year time intervals, after adjustment for simultaneous changes in other lifestyle factors including other aspects of diet, smoking status, and physical activity Scientists concluded that intake of food rich in flavonoids may contribute to weight maintenance in adulthood and prevent obesity.119 The use of herbal or alternative medicine as therapeutic supplements for neuropathy diseases has garnered rising interest in recent years. The Internet is a ubiquitous source of information/market for these supplements. A study investigated 184 websites, 28% claimed to decrease CKD (chronic kidney diseases) progression, 60% did not advise to consult a doctor before taking the supplement, and >90% did not mention any potential drug interaction, disease interaction, or caution in use during pregnancy or in children. Regulation of these products must change to prevent patient harm and misinformation.120

DIETARY SUPPLEMENTS AND PREVENTION OF CANCER:-

Dietary supplements are widely used among patients with cancer who perceive them to have strong anticancer and antioxidant properties. Large-scale, randomized cancer prevention trials have mainly been negative, with some notable adverse and beneficial effects. These trials showed that βcarotene increaseδ the risk of lung and stomach cancer, vitamin E increaseδ prostate cancer and colorectal adenoma, and selenium reduced gastric and lung cancer in populations with low selenium levels but increased rates in those with higher levels. Both β-carotene and vitamin E supplementation increase overall mortality. A recent review examined phase II and III trials that investigated the effects of multivitamins, antioxidants, vitamin D, and n-3 supplements on outcome and toxicity from cancer treatments. Although vitamin E and β-carotene reduced toxicity from radiotherapy among patients with head and neck cancer, it has been found to increase recurrence, especially among smokers. Antioxidants have mixed effects on chemotherapy toxicity, but there are no data on outcome. Vitamin D deficiency is relatively common among patients with cancer, and ongoing phase III trials are studying the effect of vitamin D on outcome as well as optimum vitamin D and calcium intakes for bone health. Docosahexanoic and eicosopentanoic acid supplements have mixed effects on cachexia and are currently being tested as potential adjuncts to maximize response to chemotherapy. Dietary supplementation tailored to an individual's background diet, genetics, tumor histology, and treatments may yield benefits in subsets of patients. 121,122 In the last decade numerous studies investigated the anticancer properties for Resveratrol (antioxidant polyphenol in red wine). Studies in experimental animals showed that resveratrol can protects against angiogenesis, inflammation, and cancer, but dietary sources of resveratrol are not enough to have an impact on health. Pre-clinical findings have provided mounting evidence that resveratrol may confer health benefits and protect against a variety of medical conditions and cancer, but there is no consistent evidence. Most of the studies that have investigated the effect of resveratrol administration on patient outcomes have been limited by their sample sizes for diseases, such as cancer, diabetes, neurodegeneration, CVDs and other age-related ailments. There is an open question as to resveratrol supplementation for therapeutic anticancer benefits, especially for prostate. 123 The relationship between dietary polyphenols and the prevention of prostate cancer has been examined by a great number of clinical trials. Although results are sometimes inconsistent and variable, there is a general agreement that polyphenols hold great promise as chemopreventive agents for the future management of prostate cancer, including resveratrol. Dietary supplements of polyphenols can act as key modulators of signaling pathways and affect post-translational modifications and microRNA expressions.124

Dietary supplementation for cancer prevention or for therapeutic intervention (market claims not consistent with supplements) has become a multibillion-dollar industry all over the world. There is a widespread belief that nutritional supplements can ward off chronic disease, including cancer, although there is little to no scientific evidence. To the contrary, there is now evidence that high doses of some supplements increase cancer risk. Despite this evidence, marketing claims by the supplement industry continue to imply anticancer benefits. Scientists and medical professionals agree that insufficient government regulation of the marketing of DS products resulted in unsound advice to cancer patients and consumers. According to the most recent National Health and Nutrition Examination Survey (2003– 2006), 50% of the US adult population uses one or more dietary supplements; most of those are multivitamin and/or multimineral supplements despite the results of observational studies that provide little evidence that multivitamins reduce cancer risk, and there have been no randomized studies of multivitamins for cancer prevention.125

CONCLUSION:-

Scientists and health professionals agree that dietary supplements (DS) can be under certain conditions

beneficial to human health, but should not replace complete and balanced daily meals of foods. For the last decades informed medical agencies, doctors, pharmacists and nutritionists inform the consumers that there's a lot of wrong information in the global supplements market. Many DS even in developed countries managed to escape the safety tests, labeling and health regulations. Scientists in the USA and Western Europe specializing on nutrition, metabolism and epidemiology reviewed the evidence for DS supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Results from Randomized Control Trials of DS showed that the majority are negative for health benefits or for preventing diseases. Self-prescription of DS should be avoided and patients, older people, pregnant women, young and people with disabilities should be informed and advised by their doctors or pharmacists for dietary supplementation.

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