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A Review on Potential Toxicity of Artificial Sweetners vs Safety of Stevia: A Natural Bio-Sweetner

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Abstract
Artificial sweeteners have increasingly become an area of controversy in the world of food and nutrition. Consumers are oftenly barraged with a number of contradictory opinions and reports regarding the safety and efficacy of sweeteners. Artificial sweetener consumption may cause migraines or headache, skin eruptions, muscle dysfunction, depression, weight gain, liver and kidney effects, multiple sclerosis and blurred vision. But on the other hand natural sweetners like stevia and its products are safe and don't cause any health problem. So it's important for the consumer to choose sweeteners with great care.
Keywords: Stevia, Artificial Sweeteners, Health Problems, Natural Sweetners, Safety Issues.

Objectives
Based on valid research, this review aims to provide concrete information on the effects associated with consumption of artificial sweeteners in comparison with stevia which is natural and no side effects on human health. Much anecdotal information is available regarding the effects of artificial sweeteners on human health. A proper understanding regarding effects of sweetners on human health and the difference between natural and artificial sweeteners will help readers and consumers to construct a healthy diet plan and select more suitable sweetners for daily life consumption.

Introduction
Sweet taste is universally regarded as the most pleasant experience as human being is born with a likeness for sweets. This preference of sweetness may encourage our ancestral primates to choose energy dense foods and possibly prevent starvation by storing extra calories in the body (American Dietetic Association, 2004).
Sweeteners are food additives that are used to improve the taste of everyday foods. Natural sweeteners are sweet-tasting compounds with some nutritional value; the major ingredient of natural sweeteners is either mono- or disaccharides. Artificial sweeteners, on the other hand, are compounds that have very little or no nutritional value. But the role of sugar in diet and its effects on our lives remains a very controversial topic.
Pakistan has very strong tradition of use of sweets at all occasion and many people blame sugar as the main reason of increase in body weight and diabetic patients in the country. Alongwith many other factors in developing countries *Diabetes mellitus* is the fourth major cause of death and currently Pakistan rank at seventh position and upto 2050 it is expected to move at fourth position (Khuwaja *et al.,* 2003). It is believed that the people of Indo-Pak born with a great liking of sweets and it remains with them from birth to death so only a few people think that they can resist the taste of sweet foods. According to a report, increase of obesity in the world among adult women and men is 35.5% and 32.2% respectively (American Medical Association, 2010). Furthermore, 68% of deaths occur in overall world due to diabetes in 2007 as diabetic patients are 2-4 times more likely to have a heart attack (Centers for Disease Control, 2007).
Today in the era of 21st century world got changed and people are becoming more conscious about their diet and health. More people than ever are dieting or reducing calories to cope with the chronic diseases. Hundreds of new diets are introducing every year to reduce the millions of extra pounds of body weight. A very popular and easy method of reducing body calories is to switch from high caloric to low caloric artificially sweetened beverages and food products.
Artificial sweeteners have increasingly become an area of controversy in the world of food, health and nutrition.

Consumers are oftenly barraged with a number of contradictory opinions and reports regarding the safety and efficacy of artificial sweeteners. Most commonly diet conscious, obese and diabetic patients use low caloric and sugar-free products for lowering calories and controlling blood glucose level. Registered Dietitians (RDs) are responsible for providing true, right and accurate information about sweetners to their patients for routine use in different food products. Numerous conflicting reports arose many questions and doubts about the use and safety of artificial and non-nutritive sweeteners in daily life.

Further, electronic media plays an important role to create awareness among masses about a problem and influencing the people towards new developments (Scheufele, 2007). These problems in media are discussed in communication sciences not health science (Chilton and Ilyin, 1993; Scheufele, 1999; Nisbet and Mooney, 2007).Medicinenet.com a website purports the following side-effects with artificial sweetener consumption: migraines or headaches, skin eruptions, muscle dysfunction, depression, weight gain, liver and kidney effects, blurred vision, multiple sclerosis, and fibromyalgia-like symptoms (Table 1). They also claim the compounds to be carcinogenic and allergenic (MedicineNet.com, 2010).

Some scientists also suggest that consuming artificial sweeteners can produce significant changes in appetite resulting in weight gain due to increased calories intake (Rogers *et al*., 1988). Furthermore, some health care professionals and scientists suggest that long-term use of artificial sweeteners needs more research in order to be approved for everyday use. Although a majority of websites and sources are not backed with peer reviewed scientific articles, most consumers get their information from simple internet searches and start using artificial sweetners without any consultancy.

Natural sweeteners as compared to artificial sweetners are thought to be safe because their extracts are derived from plants. Stevia which is a natural sweetener has become increasingly popular in the last few years, marketed as an all-natural sweetener and as an alternative to artificial sweeteners.

The purpose of this review is to gain knowledge about the different kinds of existing sweeteners, their composition, their effects on human health and comprehensive comparison between natural and artificial sweeteners to help readers during constructing a healthy diet plan and make educated decisions when using products containing sweeteners.

Artificial Sweeteners:

Artificial sweeteners are sweeteners that are derived from a chemical synthesis of organic compounds which may or may not be found in nature. Artificial sweeteners are relatively new and their uses are being researched and extended every day. Artificial sweeteners could be classified into to two types on the basis of energy value.

1- Nutritive Sweetners
2- Non- Nutritive Sweetners

- The nutritive sweeteners are mostly mono-saccharides polyols (xylitol, and sorbitol) and disaccharide polyols (lactitolm and maltitol). Energy of these are equal to sucrose (Dills, 1989).
- The non-nutritive sweeteners contain compounds from different chemical classes that feel sweet in taste and sweeter then sucrose 30-13,000 times.

Summary of the Toxicity Cause by Artificial Sweeteners

Common Name	Acute	Chronic
Acesulfame-K	Headache	Genotoxic, Thyroid tumors in rats.
Aspartame	Headache, Dizziness, Dry face, Nausea, Vomiting	Leukemia in rats.
Cyclamate		Testicular atrophy and bladder cancer in mice.
Neotame	Hepatotoxic at high doses, Headache	Weight loss, Lower birth rate.
Saccharin	Diarrhea, Vomiting	Cancer in breast fed animal offsprings, Low birth weight, Hepatotoxicity, Bladder cancer.
Sucralose	Diarrhea	Thymus shrinkage in rats.

Table 1: (Christina *et al*., 2008)

Aspartame (APM):

Aspartame (APM)) is composed of methyl ester of the dipeptideL-L-aspartyl-L-phenylalanine with molecular weight of 294.3 and a source of 4 kcal/g of energy (Food and Drug Administration, 2006). APM was discovered accidently by G. D. Searle in 1965 during working on gastrin hormone for the treatment of gastric ulcers (Mazur, R.H. 1984).

APM is the most used artificial sweetener in the world (Fry, 1999). It is found to be 200 times sweeter than that of sucrose and since 30 years it is using in different food products as a food additive. According to a report over

200 million people all over the world use APM as an artificial sweetner (Aspartame Information Center. 2009). The total world production of APM is more than 16,000 tons per year (USA Food Navigator, 2009) and among those only United States consumption is more than 8000 tons per/year (U.S. National Library of Medicine. 2006). As a sweetner APM can be found in 6000 products including carbonated soft drinks, chewing gum, candies, desserts, yogurt, table top sweetener and many pharmaceutical products such as sugar-free cough drops and vitamins (Butchko and Stargel, 2001).

So far, aspartame is the most controversial artificial sweetener due to its potential toxicity problem. Under different studies it is found to be toxic and cause different problems (Beverage Institute for Health and Wellness, 2006; Filer and Stegink, 1988; Butchko and Stargel, 2001; Brassard and Poirier, 2007; Filerand and Stegink, 1988; Lieberman *et al*., 1988; Roberts, 2007; Soffritti *et al*., 2007; Stokes *et al*., 1991). It causes acute problems like dry mouth, headache, mood change, dizziness, vomiting, nausea, reduced seizure threshold and chronic problems like lymphomas and leukemia.

The genotoxic effects of the low calorie sweetener aspartame (ASP) was investigated using chromosome aberration (CA) test, sister chromatid exchange (SCE) test, micronucleus test on human lymphocytes (Rencuzogullari, 2004). Results showed significant increase upto 2.5-4.2 folds in chromosomal aberration and in the percentage of cells in bone marrow with increasing dose of the sweetener (Mukhopadhyay *et al*., 2000). Migraines affected women were reported in a case study ages 26, 32, and 40 years while chewing aspartame additive popular chewing gum (Blumenthal, 1997). In 2007 four individuals experienced thrombocytopenia attributed to aspartame containing products consumption (Roberts, 2007). Aspartame dose of 2-100 mg/kg found involve in increasing phenylalanine without significant effects on cognitive performance (Filer & Stegink, 1988; Lieberman *et al.*, 1988; Stokes *et ai.*, 1991).Increase incidence of brain tumor was reported in USA between 1970-1980 linked with environmental origin (Olney, 1996). Consumption of aspartame can cause elevations of phenylalanine in the brain (Mayer and Wurtman, 1987) so we should needed extreme care in our daily life.

ACESULFAME-K (Ace-K):

Ace-K is reported 200 times sweeter than sugar and its sweetness similar to aspartame (Donnell, 2005). It is non-caloric as body does not metabolize Ace-K and about 95% of the consumed sweetener is excreted (Calorie Control Council, 2007). Its chemical formula is 6-methyl-1-2-3-oxathiazine-4(3H)-1-2-2-dioxide. German scientists Clauss and Jensen discovered this sweet compound in 1967 while working in the Nutrinova Lab (Nabors, 2001). The FDA approved Ace-K for beverage industry consumption in 1998. It was approved in 2003 for general public use and consumption except in poultry and meal (FDA, 2006). Acceptable daily intake (ADI) of Ace-K is 15mg/kg of body weight per day. It is available in market with Sunett and Sweet One brand names and use in different food products like frozen desserts, breath mints, candies, baked goods, cough drops and beverages.

Numerous American scientists opposed the addition of Ace-K to sweeten beverages. These scientists asserted that the studies on which the Ace-K was approved were seriously flawed. They claim that increasing the public consumption could lead to danger and health risks. The Center for Science in the Public Interest (CSPI) a non-profit agency to protect the public filed a protest with the FDA and repeatedly expressed concerns that acesulfame-K is a potential carcinogen. Dr. Michael Jacobson, Lisa Lefferts and Anne Garland of CSPI published a book in 1991 titled as Safe Food: Eating Wisely in a Risky World. In it they say that acesulfame-K is the worst artificial sweetener approved by the FDA (Jacobson *et al*., 1991). In the FDA final report 59 FR 61538 on acesulfame-K methylene chloride is mentioned as a compound formed in the initial manufacturing step and is also known as a toxic carcinogen (Mercola and Pearsall, 2006). Side effects of chronic exposure include headaches, depression, mental confusion, bronchitis, liver effects, nausea, loss of appetite, visual disturbances and cancer in humans. In 1997, scientists of Indian reported that Ace-K cause mutation in mice bone marrow cells (Mukherjee and Chakrabarti, 1997).

Cyclamate:

Cyclamate was discovered in 1937 by Michael at the University of Illinois, USA with some bitter aftertaste (Audreith and Sveda, 1944). It is derived from N-cyclo-hexyl-sulfamic acid (CHS). It is 30 times sweeter than sucrose and used in beverages and other food industry as an artificial sweetner. It is soluble in water as well as in alcohol (Sain and Berman, 1984) and very stable than other sweeteners (Barlattani, 1970). It was banned in the United States in 1970 due to associated health problems (Bopp and Price, 1991).

Metabolite product of cyclamate is cyclohexylamine reported to be rather toxic (Renwick, 1986, 2006). Recent studies shows individuals convert cyclamate to cyclohexylamine during long-term consumption (Renwick *et al.,* 2004) and high dose cyclohexylamine cause testicular atrophy in rats (Serra-Majem *et al.,* 2003). Other problems associated with its consumption are cardiovascular and nervous system problem, reduced growth rate, bladder cancer, thyroid adenoma, abnormalities in red, leukocyted, monolayer, bone marrow and germ cells (**Fitzhugh**, *et al.*, 1951; Nees and Derse, 1965; Kojima and Ichaibagese, 1966; Stoltz *et al.,* 1970; Legator *et al.,* 1969; Rosenblum and Rosenblum, 1968; Yamamura *et al.,* 1968).

Neotame:

Neotame, a derivative of aspartame is the most recent artificial sweetener. It is approved by FDA in 2002 (USFDA, 2002). It is zero caloric (European Food Safety Authority, 2007) and 6000-10,000 times sweeter than sucrose as well as 30-60 times sweeter than aspartame (Nofre and Tinti, 2000). French scientists Nofre and Tinti invented it as a derivative of dipeptide phenylalanine and aspartic acid. Its molecular structure is very much similar to aspartame. As a sweetner it is using in different food products including soft drinks, jellies, processed fruits, syrups, chewing gum, gelatins as well as cooking and baking applications due to good heat resistance.

Nofre and Tinti (2000) assert that over 90% of the neotame is excreted from the body in the form of fecal material and urine. However, a small amount is absorbed and metabolized. Two articles published reports change in body weight with the consumption of this sweetner due to toxicity, poor palatability resulting decreased food intake (Flamm *et al*., 2003; Mayhew *et al,*. 2003).

Saccharin:

Saccharin is reported 300 times sweeter then sucrose (Bizzari *et al.*, 1996; FDA, 2006). It decomposed at 228°C in acid (Lide, 1997) and above 300°C in sodium and calcium salts (Mitchell and Pearson, 1991). Saccharin was accidentally discovered by Remsen and Fahlberg as the first artificial sweetener in 1878 (Arnold, 1983). It was used widespread until World War I due to saccharin's low production cost and shortages of pure cane sugar (Weihrauch and Diehl, 2004).

Arnold studied two generation saccharin bioassays. Results showed that humeral antibody production in rats is seriously affected that may lead toward cancer. In 1977 FDA proposed a ban on saccharin use due to cancer reports in laboratory rats (Arnold, 1984; Tisdel *et al*., 1974; Schoenig *et al*., 1985; Taylor *et al*., 1980). In 2000 ban is overturned (Calorie Control Council, 2007) but it is still ban in Canada (Health Canada, 2007).Exposure to pure saccharin supported its role in pathogenesis of the liver damage (Negro *et al.*, 1994). Several studies have been done which shows association between bladder cancer and saccharine (Fukushima *et al.,* 1986; Shibata *et al*., 1989; Cohen *et al.*, 1991; Ito *et al.*, 1983; Fukushima *et al*., 1983; Fukushima *et al.*, 1986). All of the ingested saccharin after circulation in blood excreted through urine from body (Sweatman *et al*., 1981)

Sucralose:

Sucralose is zero caloric and 600 times sweeter than sucrose (International Food Information Council, 2005; Goldsmith *et al*., 2000; Goldsmith and Merkel, 2001). Its molecular weight is 400 (sucralose Food Additive Petition, 1987). Taste of sucralose is similar to cane sugar and don't have any after bitter taste (Wiet and Beyts.1992; Kuhn *et al*., 2004). This compound was accidentally discovered in 1976 by two researchers working for Tate and Lyle, a sugar refiner based company in the United Kingdom and found this new compound to be exceptionally sweet (Molinary and Quinlan, 2006; Roberts *et al.,* 2000). Its brand name is splenda and approved by FDA in 1999.

Research on animals i-e mice, rats and rabbits had shown that sucralose causes many problems like enlarged liver and kidneys, shrunken thymus glands (up to 40%), Increased fecal weight, atrophy of lymph follicles in spleen and thymus, decreased red blood cells, reduced growth rate, extension in the pregnancy period, hyperplasia of the pelvis, aborted pregnancy and diarrhea (Bowen, 2003). Bigal and Krymchantowski (2006) reported sucralose triggered migraines. Component of sweetner chemical structure 6-chloro 6-deoxyglucose is responsible for inducing anti-fertility in rats (Finn & Lord, 2000). Japanese claimed that ingested sucralose induces DNA damage in gastrointestinal organs (Sasaki *et al*., 2002). Reports of different studies have showed strong association between ingestion of sweeteners and hepatoxicity, nephrotoxicity, fetal development and retardation of placental (Arruda *et al*., 2003; Portela & Azoubel, 2004; Martins *et al*., 2005; De Matos *et al*., 2006; Portela *et al.,* 2007).

Natural sweetener

Natural sweeteners are sweet tasting compounds extracted from plants or natural products with some nutritional value. No chemical modification is done during the extraction process of natural sweetners. Natural sweeteners are very famous among masses and their production and extraction processes has been modified and perfected over time.

Stevia:

Stevia *(Stevia rebaudiana*) commonly known as "sweet leaf", "sweet herb" and "honey leaf" is a perennial herb belonging to the family Asteraceae. It was first discovered by M.S.Bertoni in 1887. Leaves of stevia contain around 10 sweetening glycosides, of which Stevioside (3–10%), Rebaudioside A (13%), and Rebaudioside B, C, D are more important (Yoshida, 1986). The main producing countries of stevia are China, Thailand, Paraguay, Taiwan, Malaysia, Korea, Japan and Brazil. Stevia is 250-300 times sweeter than cane sugar, zero caloric and without processing is highly safe to use (Thomas and Glade, 2010). Stevia is 100% natural sweetener because it is extracted from Stevia plant and during manufacturing process undergoes no chemical modification. This anticipates many consumers looking for healthy alternatives to sucrose sugar. Currently, Stevia is used in Brazil, Korea, Israel, the United States of America, Japan, China, Canada, and Paraguay (Singh and Rao 2005) in bakery, confectionery, beverage industry and in household products that is recommended by various researchers

(Cardello et al., 1994).

Studies have reported stevia safety for phenylketonurian (PKU) and diabetic patients compared to other sweeteners. Apart from non-calorie sweetener, it possesses flavor enhancing properties which complement to the attraction of using steviol glycosides in beverages and food products. Stevioside besides sweetness alongwith other related compounds that include rebaudioside A and dulcoside also offer therapeutic benefits i-e anti inflammatory, anti hyperglycemic, antihypertensive, anti cancer, anti diarrhoeal, immunomodulatory and diuretic actions (Chatsudthipong and Muanprasat, 2009). Steviol also function as drug modulator due to interaction with drug transporters (Goyal *et al*., 2010).

Stevia was banned in the United States in the 1990's unless labelled as a "supplement". However in 2008, two companies submitted FDA petitions to gain GRAS (Generally recognized as safe) status for 95% of higher purified Rebaudioside A (Reb A) extract. The Food and Drug Administration (FDA) released "no objection" letter to both companies (FDA, 2008) and the first products containing the rebaudiana extract appeared on shelves that year (Calorie control center, 2008). In September 2009, the French Government became the first government in the European Union (EU) to approve Stevia extracts consisting of at least 97% Rebaudioside A (Reb A) as food and beverage sweeteners. Stevioside and stevia extracts are officially approved as food additives in Korea, Brazil and Japan (Chatsudthipong and Muanprasat, 2009). The FDA asserts the safety of rebaudiana for human consumption through peer reviewed research, general and multi-generational safety studies. In 2006, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) announced a temporary accepted daily intake (ADI) of stevioside upto 5.0mg/kg of body weight (JECFA, 2006). Pepsi and Coca Cola are the two companies that patented stevia products under the trade name of PureVia and TruVia.

Effects as Sweetening Agent:

Stevia is 250-300 times sweeter than cane sugar, zero caloric and without processing is highly safe to use (Thomas and Glade, 2010). Currently, Stevia is used in Brazil, Korea, Israel, USA, Japan, China, Canada, and Paraguay (Singh and Rao, 2005) in bakery, confectionery, soft drink, beverage industry and in household products that is recommended by various researchers (Cardello *et al.,* 1999).

Antioxidant Activity:

Stevioside as a potential natural antioxidant (Stevia, 2007) have shown inhibitory properties on oxidative phosphorylation occuring in mitochondria of rat liver (Kelmer *et al.,* 1985; Bracht *et al.*, 1985). Iso-steviol inhibits endothelin -1 secretion and angiotensin-II-induced cell proliferation during attenuation of ROS (Reactive Oxygen Species) generation (Ghanta *et al.*, 2007).

Anti-Inflammatory and Immunomodulatory Activity:

Studies were carried to find the properties of stevia as anti inflammatory and immunomodulatory as a metabolite. It was found that stevioside reduces the synthesis of inflammatory mediators in LPS stimulated THP-1 cells by interfering with the NF-kappa B and IKK beta signaling pathway and it induced TNF secretion mediated through TLR-4 (Boonkaewwan *et al.*, 2006). Regarding immunomodulatory activity on our immune system it acts as stimulator for cellular immunity and phagocytic function (Sehar *et al.*, 2008).

Effect on Reproductive System:

The safety of stevia on reproduction system was tested in female rats. It was suggested that aqueous extracts of *S. rebaudiana* don't amend the reproduction of female rats (Saenphet *et al.*, 2006). So it food products could be used without any fear during pregnancy period.

Mutagenic and Bactericidal Activity:

Genotoxic study of stevioside and steviol showed no evidence of Genotoxicity. Results suggest they don't react with DNA and exhibit not any genotoxic mutilation related to human risk. (Brusick, 2008).

Anti-Hypertensive Effect:

Results of evaluation study of hypersensitive patients specify that stevia may be operative in lowering blood pressure. Stevioside causes vasorelaxation through inhibition of Ca2+ influx into the blood vessels (Ulbricht *et al.,* 2010).Stevia produces decrease in blood pressure and increase in diuretic and natriuretic effects in rats (Chan *et al*., 2006; Melis, 1996; Melis, 1995).

Anti-Hyperglycemic Effect:

Stevioside reveal beneficial effects on the glucose metabolism as it decreases postprandial blood glucose levels in type 2 diabetic patients. Stevioside and steviol has reversible insulinotropic effects in the presence of blood glucose and provoke insulin secretion via a direct action on P-cells (Jeppesen *et al.,* 2000) as well as on beta cells. Repeated oral use of stevioside disclosed delayed insulin resistance in rats on a diet having high fructose. (Chang *et al.*, 2005). So, Stevioside may be helpful in the treatment of type 2 diabetes (Chen *et al.,* 2006).

Anti-Viral Activity:

Extracts of *S. rebaudiana* exhibit anti rotavirus activity both in-vitro and in-vivo (Takahashi *et al.*, 2000). Hot water extracts of Stevia showed anti human rotavirus activity and inhibitory in vitro action for multiplication of all four strains of HRV (Takahashi *et al*., 2001).

Anti -Cancer Activity:

Isosteviol and related compounds that are produced from stevioside by chemical conversion and bacterial transformation were reported to have inhibitory action towards cancer cell growth in human (Maki *et al*., 2008).

Comparison Study of Stevia with Other Artificial Sweetners

Stevia	Artificial Sweeteners
Appetite Regulator (It promote the feelings of satisfaction)	Appetite Stimulator (It send signals to brain that stimulate appetite)
It helps in weight loss	Cause weight gain due to hunger stimulus
No major safety concern	Use of artificial sweetener cause lot of side effects.
Not ferment even at 2000 ^{0}C.	Break during cooking may lead to brain tumor as aspartame
Energy value: low (2.7 kcal/g)	Energy value: High (Aspartame 4 kcal/g)
More intensity in sweetness	Less intensity in sweetness
Cheaper	Costly
Useful and helpful in management of diabetes	Safety of artificial sweeteners in curing diabetes is not established.

Table.2 Superiority of Stevia over Artificial Sweeteners (Williams and Burdock, 2009)

Toxicology:

Results of an experiment presents that stevioside does not promote bladder carcinogenesis (Mizushina *et al.,* 2005). Stevioside dose of 2500 mg/kg of the body weight/day was found to be effective on growth and reproduction in rats (Melis, 1999). Acute toxicity studies of steviosides to rodents showed no lethality after 14 days after administration and no clinical signs of toxicity, histopathologicity and morphological changes were observed (Aze *et al.*, 1991).

Clinical Trials:

During clinical studies stevia extract shows changes in glucose, insulin and electrolytes in study of 60 healthy volunteers. Patients were tested in both catabolic and anabolic phases. Significant reductions in blood glucose were found with the 200 mg dose but not with the 50 mg dose in both anabolic and catabolic phases (Nunes *et al.*, 2007).

Conclusion:

Recent comprehensive studies on general and reproductive toxicity of stevioside demonstrate its safety at high dietary intake levels. More, there is no indication and existance of genotoxic potential and allergic reactions of stevioside (Qing Yang, 2010). In future, *Stevia rebaudiana* could become a complement to oral care in the form of mouthwash, toothpaste, chewing gum, artificial saliva and chewable tablets. Keeping in view its therapeutic benefits, it is a blessing and especially beneficial to obese, diabetic and hypertension patients.

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