



Statin and Spirulina: Will it be an Effective combination in Management of Type 2 Diabetes and it's Complications

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ABSTRACT

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Type 2 diabetes results from the body's ineffective use of insulin. Type 2 diabetes comprises most people with diabetes around the world and is associated with various complications such as diabetic retinopathy, neuropathy, nephropathy, cardio vascular diseases, depression, dementia, sexual dysfunction etc. Spirulina classified as a cyanobacteria, or blue-green algae which has been used for centuries as a food source in other countries. spirulina is also being promoted to prevent, treat, or cure several conditions, including high cholesterol, hypertension, diabetes, depression, viral hepatitis, and malnutrition. A few assertions have been tested, but most trials have been small, poorly designed, or inconclusive. Statins suppress the enzyme HMG-CoA reductase via Melvonate pathway. The health advantage of HMG-CoA reductase inhibitors is believed to expand behind their cholesterol lowering effects. Such pleiotropic effects of statins incorporate complimentary effects on endothelial function, systemic inflammation and oxidative stress. The above-mentioned effects were predicted to decrease the risk of diabetes, even though statins are supported by most patients, some study suggested it is affiliated with new onset of diabetes mellitus. Despite dispute discoveries, many studies suggest that different statins may relay distinct possibility of diabetes. The problem is, there's little or no scientific evidence to back up such claims. Hence this review is under taken to analyse the potential benefits if spirulina and statin in management of type 2 diabetes and its complications. Many previous studies were analysed thoroughly, and it was found that combination of spirulina and statin is found to reduce the diabetes and its complications.



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INTRODUCTION

Diabetes, accurately known as diabetes mellitus, is now one of the leading epidemics of this century, that had grown in prevalence by 50% within the previous ten years (Danaei *et al.*, 2011). Diabetes mellitus occurs globally but it is significantly more prevalent in developed nations.

Additionally, there are two main type of diabetes, type 1 (Insulin dependent) and type 2 diabetes (Non-Insulin dependent), even though diabetes can also attest throughout pregnancy, it can also occur

under additional conditions for example chemical or medication toxicity, hereditary disorders, endocrine disorder, insulin-receptor (IR) disorders as well as in connection with pancreatic disorder

Type 1 Diabetes

Type 1 diabetes does occur as consequence of intricate illness where environmental and genetic features result in an autoimmune reaction that remains clarified. During this course of action, the pancreatic beta cells over the islets of Langerhans were injured or demolished, leading to an individual depending solely on exogenic insulin for survival (Keenan *et al.*, 2010). The genetic base for this disorder is yet unknown. But certainly, several important genetic factors of type 1 diabetes which include alleles of significant histocompatibility locus in HLA class II histocompatibility antigen, HLA-DQB1beta chain and HLA-DRB1 loci (Nejentsev *et al.*, 2007) and recently the HLA-B39 locus, an HLA-B serotype simply accounts for many 40-50 percent of their familial clustering with T1DM.

Type 2 diabetes

Type 2 diabetes comprises most people with diabetes which consist of 85% of total cases. In this type of the disease, compensatory hyper production of insulin from pancreatic beta cells and peripheral insulin resistance might negate the decrease in islet functionality. The tissues that mostly shows decreased insulin sensitivity comprise liver, adipose tissues and skeletal muscle as a result of need for metabolism and glucose uptake. But it's increasingly believed that in many years, the comparative reduction in insulin secretion can be the last event resulting in hyperglycaemia (Kahn *et al.*, 1993).

Diabetic Complications

Diabetes is related to many complications. Severe Acute metabolic complications related to mortality and morbidity comprises diabetic ketoacidosis from increased blood sugar levels (hyperglycaemia) and coma because an effect of low blood sugar (hypoglycaemia).

This review will concentrate on managing type 2 diabetes and its various complications and the role of Spirulina and Statins in managing it. Diabetic complications have been classified as macrovascular complication (because of deterioration to the arteries), microvascular complication (because of injury to small blood vessels).

The macrovascular complications comprise cerebrovascular illness such as stroke and cardiovascular illness leading to myocardial infarction. Microvascular complications incorporate things like retinopathy, renal disorder known as nephropathy.

Effect of Statin

HMG-CoA reductase inhibitors (Statins), the best-selling pharmaceutical medication class in united states, which include atorvastatin, the bestselling pharmaceutical medication on world. Statins have been believed to possess good safety profile and possess established aid to cardiovascular illness to lots of classes, including men that are younger and elderly, female and male, in medium and high cardiovascular risk. Statins suppress the enzyme HMG-CoA reductase, initially in the Melvonate pathway (Buhaescu and Izzedine, 2007). The health advantage of HMG-CoA reductase inhibitors is believed to expand behind their cholesterol lowering effects. Such pleiotropic effects of Statins incorporate complimentary effects on endothelial function, systemic inflammation and oxidative stress. Effects of Statins could possibly be essential among individuals. The above-mentioned effects were predicted to decrease the risk of diabetes, rather many evidences recommend that the statin use might develop the risk of type 2 diabetes. Diabetogenic actions of Statins might be crucial among the patients with increased risk of diabetes. Whereas in a post-hoc investigation of two studies come up with meta-analysis, the increased possibility seems to be focused on study participants who was diagnosed with pre-diabetes (Kohli *et al.*, 2015).

Endothelial malfunction, resistance to insulin and low-grade chronic inflammation have been generally found and closely correlated in subject with impaired fasting glucose or impaired glucose tolerance (IGT) (Caballero, 2004). Decreased vasodilation in type 2 diabetes is a result of fault in cerebral nitric acid synthesis and activity. In a newly published newspaper, a study conducted on diabetic rats in which rosuvastatin therapy abbreviated endothelial function and decreased platelet regeneration (Schäfer *et al.*, 2007).

Standards of care for diabetes by the American Diabetes Association state that statin treatment must be started in patients with cardiovascular risk and risk for diabetes. Further, a target LDL of all 70 mg/dl is declared in patients who have diabetes and cardio vascular illness. All these beneficial/pleiotropic outcomes of Statins are indicated in many different disease processes: Statins are implicated in plaque reduction (Nissen *et al.*, 2004), reduction in inflammation (as noticed by means of a decrease in C-reactive protein level) (Cannon *et al.*, 2004), Shifting of endothelial dysfunction and with decreased thrombogenicity. These beneficial effects are believed to consequence of decrease in synthesis of proinflammatory nonsteroidal isoprenoid com-

pound along the blocking of Melvonic acid activity by HMG-CoA reductase (Corsini, 2007).

Effect of Spirulina

Spirulina is spiral-shaped, filamentous, Blue Green algae (cyanobacterium). The Spirulina species that are safe for human and animal consumption includes *Arthrospira plantensis*, *Arthrospira maxima* and *Spirulina fusiformis* (Thengodkar and Sivakami, 2010). Spirulina is reviewed as one among to have curative and protective ingredients of nutriment in 21st century (Marcel et al., 2011) owing to nutritional profile of Spirulina, deficient in toxicity and disease preventing effect. Since Spirulina contains large quantity of antioxidants namely phycocyanin, beta carotene, vitamins such as tocopherols, essential amino acids, microelements (such as K, Na, Ca, Mg, Fe, Zn) and polyunsaturated fatty acid (PUFA) which includes phenolic compounds and linolenic acid. Spirulina is suggested in hypertension (Torres-Duran et al., 2007), diabetes mellitus (Derosa et al., 2014), insulin-resistance (Marcel et al., 2011), and for decreasing toxicity due to drugs (Moura et al., 2011).

Spirulina as antioxidant

Antioxidant activity is one among the main characteristics of Spirulina. Free radicals are not only problematic to atmosphere but also source of problem inside the human body. Free radicals, which is unstable are the result of normal cellular process. These free radicals cause injury to cells which ultimately results in cell death. Through direct or indirect mechanism, oxidative stress leads the way to multiple disorders which includes rheumatoid arthritis, atherosclerosis, cancer, stomatitis etc (Desai and Sivakami, 2004). High quantity of tocopherol and beta carotene in Spirulina makes it very fine source of antioxidant. The antioxidants present in Spirulina could become pro-oxidants which defends the human body from oxidative stress (Desai and Sivakami, 2004) iron chelation effect of Spirulina was turned up during the in-vitro explosion of human neuroblastoma cells to unsafe amount of iron and to Spirulina, which showed reduction of iron instigated oxidative stress.

Antihyperglycemic effect

Anti-diabetic action of Spirulina might be because of NADPH and NADH down-regulation. The increased action of Glucose-6-phosphatase produce H^+ which attach with $NADP^+$ leads to formation of NADPH, a cofactor useful in production of carbohydrate and fat. Due to cellular activity, glycolysis will be moderate but still the pentose phosphate pathway in liver remains active. This leads to breaking of glucose

that provide NADPH, which form long chain fatty acid from acetyl radicals. Spirulina might be able to oxidize NADPH. Increased activity of hexokinase in Spirulina administered rats indicates an increased glucose uptake by liver cells. The enzyme activities indicate increased lipid metabolism is turned up to carbohydrate metabolism and elevate the glucose utilization in peripheral tissues. The potential action of Spirulina might be due to suppression of endogenous lipid synthesis. High reduced glutathione to oxidized glutathione is due to the reduced action of glucose-6-phosphate via pentose phosphate which results in transfer of NADPH to NADP (Bopanna et al., 1997). Apart from this, increased synthesis of $NADP^+$ leads to suppression of lipogenesis which lowers the tissue oxidation and diabetic resistance.

Cardio Vascular benefits

Cardiovascular (CV) benefits of all Spirulina usage are described in several papers. A review recognized several reports indicating the Spirulina (*Arthrospira*) might possibly have a favourable effect in preventing cardiovascular diseases. Decrease in plasma lipid concentrations and blood pressure, mainly triacylglycerols and low-density lipoprotein-cholesterol are proven because of oral intake of Spirulina. Spirulina has additionally been demonstrated to concomitantly modify total cholesterol and high-density lipoprotein-cholesterol (Juárez-Oropeza et al., 2009). A trial confirms that above referred review in a sample of the people. Results demonstrated that total cholesterol and triacylglycerols were considerably diminished in the Spirulina category, also HDL C levels found a significant growth, while the two systolic and diastolic Blood pressure diminished. Again, Spirulina revealed a hypolipidemic effect (Torres-Duran et al., 2007). Back in Korea, there has been a clinical trial done in elderly women and men, to find the action of Spirulina intake on immune markers, in addition to on blood lipid profiles as well on antioxidant capacity. Compared to placebo in this trial, Spirulina was found to reduce cholesterol and raised interleukin-2 and reduced interleukin-6. Spirulina had a positive influence on lipid profiles, along with antioxidant capacity in older, healthy females and men. The researchers concluded that Spirulina is acceptable as a functional food (Park et al., 2008).

RESULTS AND DISCUSSION

Diabetes complications not only decrease the duration and quality of life but also accountable for health care expenses that are enormous. More than

50 percent of those 194 million people afflicted by diabetes mellitus usually unaware of the disorder. As stated by the modern projections of this World Health Organization, India already directs the world with the most significant quantity of diabetic subjects (about 40-million), also it's predicted that number will reach nearly 80 billion by the year 2030. This will represent approximately 20 percent of the world's entire diabetic population. A population-based study shows an increasing incidence of diabetes within the metropolitan regions of India with amounts ranging from 12 and 16 percent (Mohan *et al.*, 2009).

A cyanobacterium, Spirulina, is becoming a health food also it has been commercialized as a nutritional food supplement for human. It's gaining increasing focus on the treatment of a variety of diseases. A study conducted by Mani *et al.* (2000) indicates a gradual reduction in fasting blood sugar following 2g/day Spirulina diet for 21 days. Diabetes mellitus is characterized by metabolic disorder which is further affiliated with modified action, related to liver function test enzymes such as serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), serum glutamic pyruvic transaminase (SGPT), etc. Vats *et al.* (2001) reported that reduced content of liver associated enzyme would be probably due to deficiency of insulin and linked to glycogenolysis deterioration. Decrease in SGPT, SGOT, total bilirubin and ALP levels were recognized post treatment with insulin-like protein and crude extract of Spirulina and this may be due to normalizing of liver enzyme system. Spirulina contains beta-carotene, a vitamin A precursor, is well known for its hepatoprotective activity due to its anti-oxidant profile.

Despite raised awareness, cardiovascular diseases (CVD) is major root of death in well developed countries and increased cholesterol level is one of the risk factors in developing atherosclerosis. In first human investigation by Nakaya *et al.* (1988) with 4.2g/day of Spirulina given to 15 volunteers for 8 weeks. It was observed that there was a remarkable decrease in low density lipoprotein (LDL) and atherogenic effect (Nakaya *et al.*, 1988). Another study gave Spirulina for ischemic heart disease individual and found a gradually decrease in Triglycerides, low density lipoprotein (LDL) cholesterol, and blood cholesterol level and a hike in High density lipoprotein (HDL) cholesterol level (Ramamoorthy and Premakumari, 1996).

statin can decrease the cardiovascular events and extensively used in management of diabetes. Statins extend multiple outcome in insulin sensitivity i.e.

it can Ameliorate or reduce the insulin sensitivity, but it's not explained clearly. A study by Nakata *et al.* (2006) found that Atorvastatin increased the glucose transporter-4 (GLUT-4) expression in adipocytes, reducing glucose tolerance. Study by Mita *et al.* (2007) revealed less beneficial effect in beta cells by atorvastatin as compared to pravastatin. The distinctive action on insulin sensitivity were connected to various range of lipophilicity in Statins. Pravastatin has increased hydrophilicity, but it lacks some steric interaction with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme decrease its capacity to get in and suppress cholesterol cascade by-product in non-liver cells.

Statins are most prescribed drugs, which is having accepted beneficial effect in cardiovascular risk patient. Even though Statins are supported by most patients, some study suggested it is affiliated with new onset of diabetes mellitus (Preiss and Sattar, 2011). Despite dispute discovery, many studies suggest that different Statins may relay distinct possibility of diabetes (Preiss and Sattar, 2011) pravastatin, in animal models reveals high level of adiponectin, decreases gluconeogenesis and increased insulin synthesis, on other side simvastatin decreased insulin synthesis while lovastatin and atorvastatin decreased glucose tolerance (Preiss and Sattar, 2011).

Statins reduce cardiovascular events in both key prevention and high-risk individuals. Apart from this, the preference for statin treatment in diabetic patients should depend on cardiovascular risk but not only on low density lipoprotein (LDL) level.

CONCLUSIONS

Both the Spirulina and statin were found to exert various beneficial properties. In this review several areas of research works were examined thoroughly, and many studies were found to be positive results. As discussed above it was found that Statins and Spirulina exhibited a diverse beneficial effect for the treatment of diabetes and its complications, both at the preclinical and clinical level. Therefore, for futuristic study we can conclude that drug combination of Statins and Spirulina could be a beneficial approach for the management of type-2 diabetes and its complications.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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