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Probiotics and Cardiovascular Disease

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Degree Master of Science

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Probiotics and Cardiovascular Disease

Abstract

Cardiovascular disease is the leading cause of mortality worldwide, regardless of gender. Prevention is key in decreasing morbidity and mortality. Because of this, prevention is geared toward decreasing the risk factors of cardiovascular disease. Some risk factors cannot be avoided such as family history, genetics, or gender but there are many risk factors that can be avoided or modified. These risk factors include hypertension, hyperlipidemia, obesity, tobacco use, sedentary lifestyle, and an unhealthy diet. The case report presented is a post-menopausal female with hypertension. Other than hypertension she has several other risk factors for cardiovascular disease such as a positive family history, unhealthy diet, and borderline high cholesterol. Treatment and prevention of her cardiovascular risk factors include controlling her blood pressure and cholesterol. Interventions include lifestyle changes, such as dietary modifications and exercise, and blood pressure medication. Probiotics are discussed in this report as part of diet modification for the female patient. New research has been found linking probiotics to their ability in regulating blood pressure, cholesterol, and a healthy weight through the modulation of the gut microbiota. Studies have shown the therapeutic and cost-effective potential of the use of probiotics in managing cholesterol and hypertension in the future. Further studies are warranted to determine what probiotic strains and the amount needed to be ingested to gain the greatest cardiovascular benefit.

Background

Cardiovascular disease is the number one cause of the death worldwide for both men and women (World Health Organization, 2016). Cardiovascular disease encompasses diseases that affect the vasculature of the heart and blood vessels which includes but are not limited to

coronary artery disease, cerebral vascular disease, and peripheral arterial disease. Cardiovascular disease can significantly be prevented with interventions to target the risk factors of cardiovascular disease (World Health Organization, 2016). Some risk factors for cardiovascular disease are not modifiable, such as male gender, advancing age, family history of cardiovascular disease, and being African American. Modifiable risk factors include hypertension, tobacco use, sedentary lifestyle, and hyperlipidemia. Other factors that contribute to cardiovascular disease are obesity, stress, and Diabetes mellitus (Dunphy et al., 2015). The modifiable risk factors are what is targeted by therapeutic measures. Regular physicals are necessary to identify cardiovascular risk factors or problems such as with monitoring blood pressure and cholesterol so that lifestyle changes and medications can be started to protect cardiovascular health (Direnzo, 2013).

The increased prevalence of cardiovascular diseases is mostly due to the inadequate and unsuccessful use of preventative interventions. Therefore, there is a dire need to continue developing innovative strategies to both prevent and treat cardiovascular disease. Proper diet and nutrition are crucial in decreasing the risk of cardiovascular disease and to protect and enhance cardiovascular function in those already with cardiovascular disease. New research is showing that probiotics may have the ability to reduce both cholesterol and hypertension, two major risk factors of cardiovascular disease, through the modulation of the gut flora or microbiota. An impaired balance of the gut microbiota has also been linked to obesity another risk factor for cardiovascular disease. This suggests that rebalancing the gut microbiota makeup with the use of probiotics may contribute to the ability to maintain a healthy weight and metabolism (Yadav & Jain, 2013). The use of probiotics may be able to positively influence cardiovascular health

through many different avenues especially when used in conjunction with other lifestyle and diet modifications.

Case Report

Kathy is a 67-year-old female that presents to the clinic for a follow up on her hypertension. Three weeks ago, she started on Lisinopril 20 mg daily. Her blood pressures at home has been running in the 150s to 160s systolic and the 70s to 80s diastolic. However, since starting on the Lisinopril she has developed a dry cough that she describes as annoying. It wakes her up at night. It occurs off and on throughout the day. She denies any shortness of breath, dizziness, or chest pain. She also denies any recent upper respiratory infection, nasal congestion, or nasal drainage. Her cholesterol was checked six months ago which was borderline. The only other medication she is taking is a Multivitamin daily. She has no known drug allergies. She has no history of cardiac issues including stroke, heart attack, or chest pain. She does not use tobacco. Her mother and father are no longer living. Her mother and father both had a long history of hypertension. Her mother had an abdominal aortic aneurism. Her dad had a coronary bypass and Squamous Cell Carcinoma. She has two children who are both healthy.

The physical exam revealed S1 and S2 at a regular rate and rhythm. No murmurs noted. PMI nondisplaced. Lung sounds clear bilaterally to posterior and anterior lung fields. Dry intermittent cough noted. No signs of respiratory distress. Bilateral tympanic membranes pearly gray. Cone of light present to bilateral tympanic membranes. Posterior oropharynx pink and moist. Tonsils +1 bilaterally. The nasopharynx is pink and non-edematous. A complete metabolic panel was done three weeks ago which was in normal range. Lipid panel checked six months ago which was borderline high. Her vital signs today were blood pressure 160/98, pulse 80, respiratory rate 20, and temperature 98.6.

Assessment is an ACE Inhibitor induced cough. Plan is to discontinue the Lisinopril today and to start Losartan 50 mg orally daily. She will return in three weeks to recheck her blood pressure and have a complete metabolic panel drawn. Explained to patient the complete metabolic panel will be done to assess how the kidneys are handling the new medication. She should continue to check her blood pressure daily and write it down. Discussed that the Losartan may need to be either increased or another medication added to her regimen since her blood pressure is still high with the Lisinopril. A lipid panel will also be rechecked in about six months. Discussed with patient that she may be able to decrease her cholesterol with lifestyle changes alone. She has started doing water aerobics three times a week which she enjoys. Encouraged to continue exercising several times a week. She also has started to eat healthier but asks for education regarding a healthy diet. Discussed the DASH diet and gave her written information. Discussed the use of probiotics as part of the DASH diet, as new evidence has showed the potential of probiotics to decrease cholesterol, blood pressure, and promote a healthy weight. She states she saw what cardiovascular problems did to her parents and she would like to avoid any for herself if possible. Discussed that modifying her modifiable risk factors with lifestyle changes such as diet and exercise will help to increase her cardiovascular health and decrease her risk factors in developing cardiovascular problems in the future.

Literature Review

Interventions to decrease cardiovascular disease and improve cardiovascular health are primarily done by modifying risk factors. There are non-modifiable risk factors for cardiovascular disease such as genetics; but there are many modifiable risk factors that if modified can decrease the risk of cardiovascular disease. These modifications include exercise, sustaining a healthy body mass index (BMI), not using tobacco, and diet changes such as

decreasing saturated fat, trans fat, and cholesterol. One of the biggest risk factors for cardiovascular disease is having a high low density lipid protein (LDL). Thus, one of the main priorities for treatment is decreasing the LDL (DiRienzo, 2013).

Coronary artery disease is the leading cause of death and high cholesterol contributes directly (Tomaro-Duchesneau et al., 2014). Elevated LDL in the blood is a precursor to high blood pressure and triggers the formation of an atherosclerotic plaque in the arteries (DiRienzo, 2013). Because of this it is necessary to continue studying different options in preventing and treating high cholesterol (Tomaro-Duchesneau et al., 2014). High triglycerides and low high-density lipid proteins (HDL) are also risk factors but are treated secondarily. Statins are the first-line medication for treating elevated LDL but should come after dietary and lifestyle modifications are ineffective (DiRienzo, 2013).

Likewise, dietary and lifestyle modifications should continue with the use of statins or other medications that lower cholesterol or blood pressure. Non-pharmacologic therapies need to be investigated because some people do not tolerate statins or they are not at high enough risk to need a statin. Non-pharmacologic therapy may not always decrease cholesterol as well as a statin but will still lower cholesterol without the side effects. Also, combining dietary modifications with medications may show the best results. In fact, dietary modifications with the use of probiotics may show similar results in decreasing LDL compared to a diet alone low in saturated fat and cholesterol (DiRienzo, 2013).

Probiotics are mostly recognized for their use in preventing diarrhea caused by the use of antibiotics. However, their ability to positively impact cardiovascular health by decreasing cholesterol and hypertension is not as well-known (Tomaro-Duchesneu et al., 2014). A meta-analysis of randomized controlled trials looked at 485 participants with high, borderline high, or

normal LDL and results showed that LDL and total cholesterol levels dropped significantly with those who ingested the probiotics compared to the control group. It is thought that gram-positive bacteria in the gut microbiota influence an increase in the catabolism of cholesterol through an enzyme called bile salt hydrolise. Bacteria that produce a high amount of this enzyme are able to break down bile salts, which are a precursor to cholesterol, so that they are excreted from the body. The body then breaks down cholesterol to replace these broken down bile salts, thus lowing serum cholesterol (Ettinger et al., 2014).

A review by Tuohy, Fava, and Viola (2014) was done to discuss this recently found association between the human gut microbiota and cardiovascular disease, as well as how the gut microbiota can be influenced by diet. Fruits, vegetables, and whole grains have long been considered part of a heart healthy diet. New research now shows that they increase the diversity of gut microbiota, since they include great amounts of fiber, prebiotics, and polyphenols. These findings suggest that it is by modifying the gut microbiota that these foods are retrieving part of their cardiovascular benefits. For example, red meat, low fiber, and high fat have long been considered the opposite of cardio protective. These foods have now been shown to decrease the diversity of the microbiota. These findings suggest that the influence on the gut microbiota may have been why these foods were shown to have a positive or negative influence on cardiovascular health.

The gut microbiota has also been shown to change depending on a host's health status. Probiotic bacteria have been found to affect the make-up of the gut microbiota. Because of this it is worth studying the cardiovascular benefits in manipulating the gut microbiota with probiotics (Ahrén et al., 2014) . Probiotic bacteria in many studies have shown to have "significant cholesterol-lowering properties" (Tomaro-Duchesneau et al., 2014, p.3). Probiotics may also

have many advantages since they are found in many natural foods such as yogurt, cheaper than most medications, and safe (Tomaro-Duchesneau et al., 2014).

According to Mistry (2014) there have been several strains of probiotics that have shown to lower LDL cholesterol. These strains include L. reuteri, E. faccium, and L. acidophilus. The effect that each one has on reducing cholesterol is variable. A meta-analysis by Zuang et al. (2012) showed that probiotics in the diet can decrease total cholesterol by 6.4 mg/dl and LDL by 4.9 mg/dl. The mechanism is not fully understood. More research is needed because it is not well known what probiotic strains and doses are needed to achieve maximum lipid lowering effects.

Probiotics have been shown to lower cholesterol through several mechanisms. One of the mechanisms being cholesterol assimilation (Tomar-Duchesneau et al. (2014). A study by Tomar-Duchesneau et al. (2014) looked at different Lactobacillus strains and their ability to assimilate cholesterol both in a culture media and simulated intestinal conditions. The results showed that all the strains had the ability to assimilate cholesterol with Lactobacillus reuteri being the best with the ability to assimilate 67% of the cholesterol. A study by Kumar et al. (2013) looked at the effect of a probiotic Lactobacillus rhamnosus in combination with Aloe Vera on rats who had high cholesterol. The study results show that serum cholesterol and LDL were decreased significantly and HDL were increased significantly. Probiotics may be a warranted dietary approach in decreasing cholesterol levels among many other health benefits.

Probiotics may also be able to decrease inflammation throughout the body which adds to cardiovascular problems. L reuteri has been shown to decrease inflammatory markers in the blood suggesting that probiotics may be able to decrease the risk of cardiovascular disease, type 2 Diabetes, and obesity. Probiotics, such as L. reuteri, should be considered an addition to a healthy diet to help manage elevated LDL and may have a place in cholesterol treatment

(DiRienzo, 2014) (Tomaro-Duchesneau et al., 2014). According to Direnzo (2014) “L. reuteri capsules are the only probiotic capsules shown to significantly lower LDL” (p.20) and suggests that more studies should be done regarding probiotics used in combination with statins.

Another risk factor for cardiovascular disease that probiotics may address is hypertension. A systematic review by Khalesi et al. (2014) was done to look at probiotics and what type of effect they have on blood pressure. Recent human studies have shown that oral probiotic intake may have a positive effect on blood pressure control. Probiotics are throught to improve blood pressure by decreasing total cholesteral, LDL, insulin resistance and acting on the renin-angiotensin system. The systematic review looked at randomized control trials and “overall, the results showed that consuming probiotics could significantly reduce systolic bolood pressure by 3.56 mmHG and diastolic blood pressue by 2.38 mm HG.” (p.901). Most of the studies used fermented milk but there were different types of probiotics used in some studies to adequately give conclusions as to what probiotic is best in reducing blood pressure. Fermented milk may have properties that act as angiotensin-converting enzyme inhibitors (Khalesi et al., 2014).

A study by Ahrén et al. (2014) examined the anti-hypertensive effect of two combined probiotics, blueberries and Lactobacillus plantarum, and the association with change in the gut microbiota. The study was done in rats and after four weeks the results showed a significant drop in blood pressure for the rats that received the probiotic compared to the rats that did not. There was also a change in the gut microbiota for the rats that received the probiotic combination. The results conclude that the probiotic product had significant anti-hypertensive effects which may also decrease the risk of cardiovascular disease.

Probiotics may act in different ways to control blood pressure. They may reduce cholesterol with one meta-analysis showing a 6.4 mg/dL decrease in total cholesterol, a 4.9 mg/dL decres in LDL, and a 3.9 mg/dL decrease in triglycerides. They may regulate the RAS by producing properties that act as angiontensin-converting enzyme inhibitors. Reducing weight also decreases blood pressure but only one study showed an association in weight loss with probiotics. Therefore probiotics may have a few different uses in decreasing the risk of cardiovascular disease. The ability probiotics have shown to improve blood pressure control and lipids potentiate the future use of probiotics in the treatment and prevention of high blood pressure and high cholesterol. Future studies are needed to examine what strains of probiotics and what amount is needed to gain maximum benefit (Khalesi et al., 2014).

Antibiotics increase blood pressure by altering the gut microbiota. Chronic systemic inflammation can be due to a decrease in gut microbiota and the inflammation can be due to or a result of hypertension (Jose & Raj, 2015). “Preeclampsia is associated with hypertension and inflammation, the incidence of which is decreased by chronic intake of probiotics” (p.404). Lactobacilli produce peptides that can inhibit angiotensin production and fermented milk when ingested has been shown to lower blood pressure in humans who have hypertension. Blueberries are also thought to decrease blood pressure by increasing the Lactobacilli in the gut (Jose & Raj, 2015).

Lastly, probiotics’ effect on the gut microbiota may positively impact weight regulation. Obesity, diabetes, high cholesterol and hypertension are the main medical conditions that influence cardiovascular risk (Ebel et al. 2014). “According to the WHO, these diseases are the leading cause of worldwide morbidity and mortality” (p.177). New research suggests that the bacteria in the gut may play a part in weight regulation since bacteria that is normally found in

microbiota positively impacts “nutrient uptake and energy regulation” (p.178). A recent study on obese mice showed that L. rhamnosus given over eight weeks reduced weight without change in food intake. “The importance of the microbiota composition in obesity has been shown in model laboratory organisms and confirmed in humans” p. (179). The effect of probiotics on decreasing hypertension has not been studied as extensively as their effect on cholesterol but there are several avenues that warrant investigation further. For example, there have been some bacteria found to make nitric oxide which could be used for the vasodilatory effect in decreasing hypertension.

In western civilization heart disease seems to go along with the chronic conditions obesity, Type 2 diabetes, and inflammation. Those who are obese have a distinct gut microbiota make up different from those who are lean. Overnutrition as well as a diet high in saturated fat, cholesteral, and simple sugars changes the gut microbiota make up. Obesity is one of the main risk factors for cardiovascular disease due to it being linked to type 2 diabetes, chronic inflammation, and hyperlipidemia. A study was done on mice that showed a decrease in weight after three weeks of Lactobacillus rhammosus or Lactobacillus sakei daily. There was no change in what the mice ate or the amount. The results show that the change in gut microbiota lead to a decrease in fat mass. A single probiotic may not get rid of obesity but understanding how the microbiota effects “adipose tissue, cholesterol, satiety and other factors associated with cardiovascular health, will contribute to identying new probiotic interventions” (Ettinger et al, 2014, p.722). Probiotics can be used to reestablish a healthy gut microbiotia of that of a lean person to hopefully lose weight and prevent the cardiovascular detrimental effects (Ettinger et al, 2014).

In conclusion, probiotics are very affordable compared to other medications such as ace inhibitors, beta blockers, and statins without the side effects. Probiotics could decrease the cost of these medications when used in combination. There is still a lot of investigating and experimental studies that need to be done on the gut microbiota and the use of the probiotics to treat and prevent cardiovascular disease but the potential is there for probiotics to become part of therapy in cardiovascular disease (Ettinger et al., 2014). Modifying risk factors for cardiovascular disease is the key to promote cardiovascular health and prevent cardiovascular disease. Probiotics may have a place in the modification of risk factors for cardiovascular disease such as high cholesterol, hypertension, and obesity. Further studies are warrented to determine the strains and amount of probiotics necessary to get cardiovascular benefits.

Learning Points

- Gut microbiota may be the new target for the prevention, treatment, and management of cardiovascular disease
- Probiotics may be able to lower cholesterol particularly low density lipid protein (LDL), decrease hypertension, and help with maintaining a healthy weight by increasing gut microbiota diversity
- Probiotics are inexpensive, have less side effects compared to blood pressure and cholesterol medications, and can easily be added to a healthy diet for example a probiotic yogurt
- Lactobacilli are the primary species shown to decrease cholesterol with L. reuteri showing the most significant cholesterol lowering capability
- The risk of cardiovascular disease can be significantly decreased through modifiable risk factors and these risk factors should be addressed at each clinical visit

References

Ahrén, I. L., Xu, J., Önning, G., Olsson, C., Ahrné, S., & Molin, G. (2014). Antihypertensive activity of blueberries fermented by lactobacillus plantarum DSM 15313 and effects on the gut microbiota in healthy rats. *Clinical Nutrition, 34*(4), 719-726. doi:10.1016/j.clnu.2014.08.009

DiRienzo, D. B. (2013). Effect of probiotics on biomarkers of cardiovascular disease: Implications for heart-healthy diets. (2013). *Nutrition Reviews, 72*(1), 18-29. doi:10.1111/nure.12084

Dunphy, L. M., Winland-Brown, J. E., Porter, B. O., & Thomas, D. J. (2015). *Primary Care: The Art and Science of Advanced Practice Nursing* (4th Edition ed.). Philadelphia, PA: F. A. Davis Company.

Ebel, B., Lemetais, G., Beney, L., Cachon, R., Sokol, H., Langella, P., & Gervais, P. (2014). Impact of probiotics on risk factors for cardiovascular diseases. A review. *Critical Reviews in Food Science & Nutrition, 54*(2), 175-189. doi:10.1080/10408398.2011.579361

Ettinger, G., MacDonald, K., Reid, G., & Burton, J. P. (2014). The influence of the human microbiome and probiotics on cardiovascular health. *Gut Microbes*, *5*(6), 719–728. http://doi.org.ezproxy.undmedlibrary.org/10.4161/19490976.2014.983775

Jose, P. A., & Raj, D. (2015). Gut microbiota in hypertension. *Current Opinion in Nephrology & Hypertension*, *24*(5), 403-409. doi:10.1097/MNH.0000000000000149

Khalesi, S., Sun, J., Buys, N., & Jayasinghe, R. (2014). Effect of Probiotics on Blood Pressure: A systematic review and meta-analysis of randomized, controlled trials. *Hypertension*, 897-903.

Kumar, M., Rakesh, S., Nagpal, R., Hemalatha, R., Ramakrishna, A., Sudarshan, V., & ... Kumar, R. (2013). Probiotic Lactobacillus rhamnosus GG and Aloe vera gel improve lipid profiles in hypercholesterolemic rats. *Nutrition*, *29*(3), 574-579. doi:10.1016/j.nut.2012.09.006

Mistry, P. (2014). Natural cholesterol-lowering products: Focus on probiotics. *British Journal of Community Nursing*, S14-8.

Tomaro-Duchesneau, C., Jones, M. L., Shah, D., Jain, P., Saha, S., & Prakash, S. (2014). Cholesterol assimilation by lactobacillus probiotic bacteria: An in vitro investigation. *BioMed Research International*, *2014*, 380316. doi:2014/380316

Tuohy, K. M., Fava, F., & Viola, R. (2014). 'The way to a man's heart is through his gut microbiota' - dietary pro- and prebiotics for the management of cardiovascular risk. *Proceedings of the Nutrition Society*, *73*(2), 172-185. doi:10.1017/S0029665113003911

World Health Organization. (2016, September). *Cardiovascular diseases.* Retrieved from World Health Organization: http://www.who.int/mediacentre/factsheets/fs317/en/

Yadav, H., & Jain, S. (2013). Herbo-probiotic therapy in cardioprotection: A new way of nature to nurture. *Nutrition*, *29*(7), 1070-1071. doi:10.1016/j.nut.2012.11.001