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Cardiovascular Disease - Is a Whole Food Plant-based Diet the Answer?

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Abstract

Objective: To determine if a whole food plant-based diet can prevent and cure cardiovascular disease.

Results: People on whole food plant-based diets exhibit extremely low levels of plasma LDL. Another risk factor for developing atherosclerosis, is inhibited production of nitric oxide, which is vital for healthy blood flow. One of the main inhibitors of nitric oxide production is asymmetric dimethyl-l-arginine (ADMA). An inverse relationship was found between dietary fat and ADMA levels. The diets with the best results were the diets where oil intake was reduced to a minimum. Clinically, people who went on whole food plant-based diets had their cardiovascular disease stabilized or improved. A possible difference was also found between a person already exhibiting symptoms of cardiovascular disease versus a healthy person. LDL only causes damage under oxidative stress and Dimethylarginine dimethylaminohydrolase, the enzyme that degrades ADMA, is also inhibited by oxidative stress. This would suggest that a diet high in antioxidants may have similar benefits.

Conclusion: A whole food plant-based diet is a good method for stabilizing and improving cardiovascular disease, especially if oil and processed foods are removed from a person's diet as much as possible. It may be possible to structure a diet based on antioxidant intake with similar effects.

Introduction

Based on the most recent data available, in 2018, the United States spent about $3.65 trillion or $11,172 per person on health care. It is estimated that by 2028 the United States will be spending $6.2 trillion or $17,611 per person on health care (Centers for Medicare & Medicaid Services, 2021). This would amount to close to 20 percent of the United States' GDP. When dividing this up by individual diseases, heart disease and stroke are responsible for more than 868,000 American deaths, which is one-third of all deaths. These diseases cost the health care system $214 billion in 2018, or 5.9 percent of the total US expenditure on health care (Benjamin et al., 2018). More than 34.2 million Americans have diabetes, and another 88 million Americans have prediabetes, which puts them at risk for type 2 diabetes. In 2017, the total estimated health care cost of diagnosed diabetes was $237 billion (American Diabetes Association, 2017). In 2017–2018, the age-adjusted prevalence of obesity in adults in the United States was 42.4% (Hales et al., 2020). It is estimated that the medical costs of obesity had risen to $147 billion per year in 2008 (Finkelstein et al., 2009). All this money is spent only after a person gets sick; to treat the symptoms. If the United States focused its efforts on the underlying causes of illness and not just the symptoms, a lot of this money wouldn't need to be spent. This paper will explore if following a whole food plant-based diet could be utilized to prevent cardiovascular disease and reverse its effects.

Methods

Data was found using google, google scholar and PubMed databases. Keywords used were whole-food plant based, WFPB, cardiovascular disease, atherosclerosis, LDL, vegan, vegan diet, ADMA, asymmetrical dimethylarginine, and antioxidant.

Discussion

What is a whole-food, plant-based (WFPB) diet, and how is it different from a vegan diet

The people who follow a vegan diet do so mostly for moral and ethical reasons, though health is also a significant factor (Janssen et al., 2016). It is worth noting that this study was done in Germany and may not apply to other countries. Those who follow a WFPB diet, the primary motivator is usually for health purposes (Wendel B., 2019). It is important to note the motivation for following a diet because that could indicate if the diet will be strictly adhered to and may help gauge how long a person would continue to follow it. The difference between the two is that someone following a vegan diet will not consume any animal products or derivatives, but any plant-based food is fine. A WFPB diet, on the other hand, is not as clear. However, the main goal is to eat plant-based (exclusively or small amounts of animal products will be allowed) and to refrain from overly processed foods. WFPB diets also recommend refraining from all processed and hydrogenated oils (Esselstyn, 2008 which does not allow any animal products). One of the most well-known benefits of plant-based diets is that they prevent and sometimes reverse cardiovascular disease.

Can a WFPB Diet Prevent and Reverse Cardiovascular Disease?

Esselstyn et al., 2014 performed a study that followed a cohort of 198 participants to determine if they could voluntarily adhere to the necessary dietary changes and to document their cardiovascular outcomes. The patients were self-selected after learning about the program through their own research. All the patients had cardiovascular disease. The participants were requested to follow a core diet consisting of whole grains, legumes, lentils, other vegetables, and fruit. They were also encouraged to take a multivitamin and vitamin B12 supplement

and to use flax seed meal, which served as an additional source of omega-6 and omega-3 essential fatty acids. They were asked to refrain from consuming all added oils and processed foods, fish, meat, fowl, eggs, dairy products, avocado, nuts, caffeine, and excess salt. Each patient was also told to avoid sugary foods (sucrose, fructose, and drinks containing them, refined carbohydrates, fruit juices, syrups, and molasses). Patients who avoided all meat, fish, dairy, and, knowingly, any added oils were considered adherent. The patients were followed for an average of 3.7 years. It is worth noting that there was no proper control group instead the non-compliant patients were used as the control group. Of the 198 participants, 177 remained compliant while 21 did not. Of the 177 compliant patients, a remarkable 90 percent remained stable or improved, while in the non-compliant group, only 38 percent remained stable while none improved. In Esselstyn, 2008, he similarly documents many personal experiences with individual patients showing similar results.

The limitation of these studies is the lack of random selection and proper control groups. Wright et al., 2017, on the other hand, performed a randomized controlled trial to assess the benefits of a WFPB diet with the same restrictions as Esselstyn et al., 2014. The limitations of this trial were that this trial only documented the risk factors for cardiovascular disease and not symptoms or clinical outcomes. Furthermore, the control versus the intervention group were only compared for the first six months. Nonetheless, the trial showed a statistically significant reduction in both the body mass index and cholesterol levels in the intervention group compared to the control group. Remarkably, the need for medications for the control group went up by 8 percent, while in the intervention group, it decreased by 21 percent in such a short period of time.

Ornish et al., 1998 conducted a randomized controlled trial from 1986 to 1992 to demonstrate the beneficial effects of a diet change on patients with cardiovascular disease. Patients were allowed fruits, vegetables, grains, legumes, and soybean products without caloric restriction. No animal products were allowed except egg white and one cup a day of non-fat milk or yogurt. Cholesterol intake was limited to 5 mg/day or less. Caffeine was eliminated, and alcohol was limited to a minimal amount. Vitamin B12 was a recommended supplement (Ornish et al., 1990). At the end of the study, there were about 0.95 cardiac events per patient in the control group as opposed to 0.50 cardiac events in the experimental group. While this is certainly a positive outcome, there was still a 50 percent chance of an adverse event per patient in the experimental group. Contrast this with Esselstyn et al., 2014, where there were only .023 events per patient in the compliant group; this number isn't great. The only difference between the two diets was that Esselstyn et al., 2014 required abstention from all animal products and oils while Ornish et al., 1998 allowed egg whites and one cup per day of non-fat milk or yogurt and didn't have any oil restrictions.

In a large prospective cohort study, it was found that even if a person is following a plant-based diet, if it is high in healthy plant foods (defined by the authors as whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee), there was a substantial reduction in coronary heart disease. However, if it is high in less-healthy plant foods (juices/sweetened beverages, refined grains, potatoes/fries, sweets), there was an increased risk of coronary heart disease (Satija et al., 2017). There are many other studies (De Lorgeril et al., 1999; Singh et al., 2002; Burr et al., 1989; Kappagoda et al., 2006; Baden et al., 2019) that investigated plant-based diets and their effects on cardiovascular disease, however, only a diet restricting all animal products and oils had an almost guaranteed positive outcome (as seen in Esselstyn et al., 2014) while the other diets, despite favorable outcomes, only had reduced risks. This suggests that eating only healthy plant-based foods is the most effective diet, as evidenced by Satija et al., 2017 and Esselstyn et al., 2014.

How does a WFPB diet help with cardiovascular disease, and what mechanisms does it target?

Cardiovascular disease is usually related to atherosclerosis (American Heart Association, 2017). Atherosclerosis is a disease where plaque gets deposited inside the lumen on the walls of arteries. The areas in the arteries that are vulnerable to atherosclerosis are where disturbed flow and consequently low endothelial shear stress (ESS) and oscillatory shear stress occur (Jolanda et al., 2012). ESS is the force per unit area exerted by blood flow on the vessel wall that depends on blood viscosity and flow velocity (fig. 1). These are usually near the branch points and along inner curvatures or regions where the uniformity of the blood flow is disturbed. The most common regions are the abdominal aorta, coronary arteries and

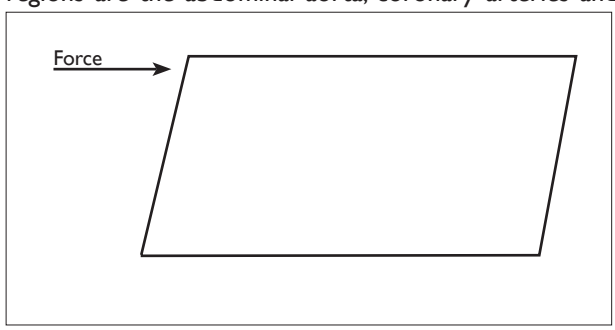

Figure 1: visual representation of shear stress

iliofemoral arteries (DeBakey et al., 1985). In contrast, arterial regions exposed to moderate physiological ESS are protected from atherosclerosis (Zarins et al.,1983). When endothelial cells are in a high ESS area (more than 15 dyne/cm¬2) they exist in an almost dormant state. They decrease their expression of vasoconstrictors, paracrine growth factors, inflammatory mediators, adhesion molecules, and oxidants while increasing their expression of vasodilators and anti-platelet factors (like nitric oxide), growth inhibitors, and antioxidants. This causes minimal proliferation and apoptosis of these cells.

Furthermore, these cells align in the direction of the blood flow. Nitric oxide (NO) is produced to maintain homeostasis because NO reduces the ESS by vasodilation and thus reduces the shear stress on the cells. On the other hand, when the endothelial cells are in a low ESS (less than 4 dyne/cm¬2) they have a greater vulnerability to factors that stimulate proliferation and apoptosis (such as oxidized low-density lipoproteins). They are in a persistent low antioxidant state and have a reduced expression of vasodilators, growth inhibitors, anti-platelet factors, and antioxidants. They increase their expression of vasoconstrictors, paracrine growth factors, inflammatory mediators, adhesion molecules, and oxidants. Furthermore, these cells present in an unorganized fashion ((Malek, 1999; Ziegler et al., 1998; Furchgott, Zawadzki, 1980). The endothelial cells attempt to maintain homeostasis and consequently a certain ideal rate of flow in the blood stream. Therefore, they will try to narrow the lumen through proliferation to raise the flow rate and consequently the shear stress to optimal levels.

Glycocalyx is a highly charged layer of membrane-bound macromolecules connected to a cell's apical membrane. This layer functions as a barrier between a cell and everything in the extracellular space. Glycocalyx also serves as a mediator for cell-to-cell interactions and protects the cell membrane from the actions of physical forces and stresses, allowing the membrane to maintain its integrity (Martinez-Seara Monne et al., 2013). Glycocalyx also behaves as a sort of lubrication layer, assisting in the movement of red blood cells through blood vessels and buffering the effect of fluid shear stress acting directly on the endothelial cell's membrane (Tarbell, Pahakis, 2006). When the endothelial cells are in a low ESS environment, the layer of glycocalyx starts to thin, thereby weakening the cells' ability to protect themselves. Furthermore, when the endothelial cells are in a low ESS environment, because of the high proliferation rate and disturbed blood flow, the cells have weaker tight junctions. They can be less functional, and thus, tend to favor the migration of lipids (specifically low-density lipoproteins (LDL)) into the subendothelial space. Furthermore, due to the thinning of the glycocalyx, the LDL begins to migrate through the endothelial cells into the subendothelial space though vesicular bodies that travel through the endothelial cells (Zmysłowski, Szterk, 2017).

After the LDL enters the subendothelial space, it begins to undergo oxidation, primarily from reactive oxygen species. First, the LDL forms minimally oxidized LDL, which has a pro-inflammatory effect on the arterial wall. The LDL is further oxidized to form moderately oxidized LDL particles, and then finally, they form aggregates of highly oxidized LDL (oxLDL). These oxidized LDL particles are recognized by macrophages that congregate around the aggregate (Zmysłowski, Szterk, 2017). These macrophages begin to break down the oxLDL into cholesterol and fatty acids. Some of the free cholesterol will be transported to the plasma membrane and then out of the cells while the rest will be re-esterified to cholesterol fatty acid esters which accumulate as a foam-like substance in the macrophages (and hence, those macrophages are called 'foam cells') (Brown et al., 1980) (Zmysłowski, Szterk, 2017). If there is a continuous supply of oxLDL, these foam cells keep ingesting it until cell death occurs. These dead foam cells form the inner lipid-rich core of the atherosclerotic lesion (Falk, 2006). It is worth noting that high-density lipoproteins (HDL) have the opposite effect and facilitate the removal of the free cholesterol from the cells and back out into the bloodstream and therefore, can reverse this process. This is the beginning of the atherosclerosis, and over time if left to progress, this plaque buildup leads to the narrowing in diameter of the lumen of blood vessels. Eventually, the lesion will attract platelets due to the roughness caused by the endothelial dysfunction. The aggregation of these platelets will cause a clot to begin to form, which can detach (thrombosis), leading to myocardial infarction, stroke, or sudden death (Khatana et al., 2020).

The Nitric Oxide Pathway and its Importance

As previously mentioned, nitric oxide acts as a vasodilator, and an anti-platelet factor. Additionally, it inhibits endothelial inflammation and inhibits smooth muscle cell proliferation (Lowenstein, 2006). The anti-platelet characteristic essentially keeps the blood flowing smoothly and aids in maintaining a stable blood pressure (Moncada, Higgs, 2006). Nitric oxide is synthesized in the endothelial cells from l-arginine by the enzyme endothelial nitric oxide synthase (eNOS). A competitor for the l-arginine binding site is asymmetric dimethyl-l-arginine (ADMA). There is another enzyme, dimethylarginine dimethylaminohydrolase (DDAH), that degrades ADMA (fig. 2). The ability of DDAH to degrade ADMA is diminished

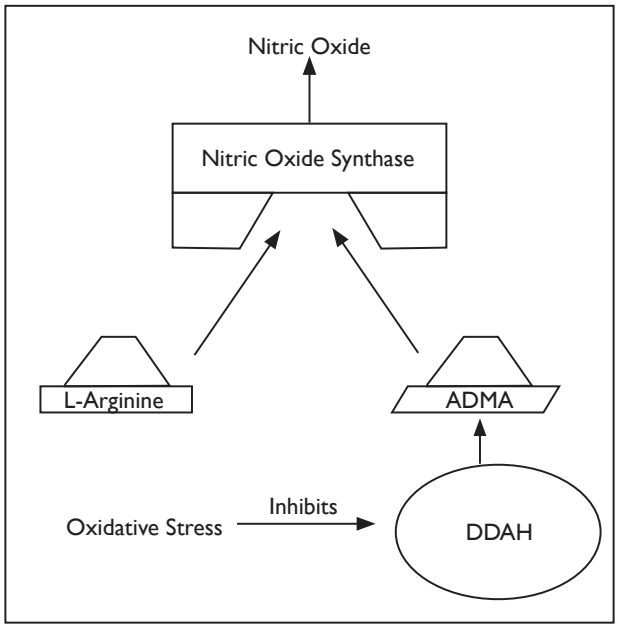

Figure 2: nitric oxide synthase and its inhibitor. (Adopted from Esselstyn C. B., 2008)

in the presence of reactive oxidizing agents, which incidentally is the same environment that LDL gets oxidized in (Förstermann, Sessa, 2012). It is no coincidence that in the presence of oxLDL plaque formation, weakened nitric oxide expression is also witnessed (Cooke 2004). Abnormally high levels of ADMA are seen in patients with cardiovascular disease (Schlesinger et al., 2016), congestive heart failure (Usui et al., 1998), hypercholesterolemia (Böger et al., 1998), hypertensive children and adolescence (Goonasekera et al., 1997), some cancers (Sulicka et al., 2012; Javadiyan et al., 2012), end-stage chronic renal failure (Vallance et al., 1992), schizophrenic patients (Das et al., 1996) and many other illnesses (Tain, Hsu, 2017).

Does a WFPB diet impact a person's ADMA levels?

Since nitric oxide is so important in maintaining proper blood flow and diminishing the risk of thrombosis by acting as an anti-platelet factor, if nitric oxide production could be improved, it would follow that the risk of thrombosis would also diminish. Furthermore, because a low ESS is an early risk factor for the formation of an atherosclerotic lesion, an increase in nitric oxide production would yield smoother flowing blood and a reduced number of low-ESS areas. Because ADMA is an inhibitor to eNOS and consequently the production of nitric oxide, it would be a reasonable target for measuring the effects of a diet that is trying to reduce the risk of atherosclerosis and subsequent thrombosis. It is also reasonable to assume that ADMA is in part responsible for these illnesses because it is well documented that abnormally high levels of ADMA are present in patients with cardiovascular disease (Schlesinger et al., 2016) (Bultink et al., 2005; Stühlinger et al., 2002; Meinitzer et al., 2007; Schnabel et al., 2005). If after following the diet, a patient's ADMA came down to normal levels, it would be reasonable to assume that this diet will help lower the risks of atherosclerosis and thrombosis. To the best of this author's knowledge, no study was performed on ADMA levels after a plant-based diet. However, in a study done on the effects of a high-fat meal (heavy cream, ice cream, safflower oil, a powdered whey protein, syrup, and Lactaid) on ADMA and vasodilation, an inverse relationship was found between the two. As ADMA levels increased (at about 5 hours after the meal), nitric oxide-mediated arterial vasodilation decreased. When a low-fat meal (whey protein, skim milk, evaporated skim milk, syrup, and granulated sugar) was given, no significant ADMA elevation was recorded (Fard et al., 2000). Even though the low-fat meal was not plant-based, it showed a direct correlation between fat consumption and ADMA levels. This would suggest that minimizing even plant-based fats would have a positive outcome. Another study was done over a 2-month period analyzing the effect of different diets on ADMA levels. What was found was that those diets high in carbohydrates caused a reduction in ADMA levels. This study also found that a change in ADMA levels did not associate with a change in the amount of fat consumed (Päivä et al., 2004). This would seem to conflict with Fard et al., 2000, who found that high-fat diets correlate with higher ADMA levels. However, regardless of this conflict, diet definitely influences ADMA levels, and more research must be done in this area to determine which foods affect ADMA levels.

A WFPB's Diets Effect on LDL Levels

It is well documented that elevated LDL levels are a major risk factor for cardiovascular disease (Castelli et al., 1977; Gordon et al., 1989; Duncan et al., 2019). Because oxLDL is a major contributing factor to the formation of atherosclerosis, lowering the levels of LDL in the blood would reduce the ability of an atherosclerotic lesion to form even if there is endothelial damage present. At current, it is recommended that total cholesterol levels should be less than 150 mg/dL and LDL levels should be less than 100 mg/dL (Grundy et al., 2018). It is worth noting that current literature suggests that dietary cholesterol does not impact a person's risk for cardiovascular disease. Rather, the dietary intake of fat (specifically saturated fats and trans-fats) is the primary cause of cardiovascular disease (Soliman 2018). This information fits with the current known mechanism of the formation of atherosclerotic lesions since it is the LDL that brings the cholesterol into the subendothelial space. This is shown by Esselstyn et al., 2014, that removing lipids from a person's

diet leads to the radically reduced risk of cardiovascular disease. Therefore, if a person has low levels of LDL, no lesion should form even if the endothelial cells were not performing optimally.

In a cross-sectional study that took place in six Slovenian regions, participants were placed into short-term (0.5–<2 years), medium-term (2–<5 years), and long-term (5–10 years) groups. Each group was instructed to follow a WFPB diet that consisted of whole grains, fruits, vegetables, and legumes, moderate intake of nuts, seeds, avocados, soy, wheat products, little or no added fats/oils (e.g., coconut, and palm fat/oil, olive oil), and the exclusion of all animal products. The participants were advised to consume a majority of starchy foods, such as whole grains, legumes, and potatoes, all prepared without oil or added fat. Participants were asked to limit portions of high fat plant foods. And it was suggested that consumption of high-fat foods be limited to 1–2 tablespoons of flax, 1–2 tablespoons of sesame seeds, 20–30 g of walnuts, hazelnuts or almonds a day. Occasionally pumpkin seeds (as part of salads, nut butters, or smoothies), and minor amounts of soy products were allowed up to 2–4 times a week (mostly as ingredients). Vitamin B12 and D3 were recommended to be taken as supplements. The mean LDL levels for groups one and two were 80 mg/dL, while group three had a mean LDL level of 70 mg/dL. Furthermore, the range was 54 mg/dL to 100 mg/dL for all participants, placing them at or below the recommended LDL levels. (Jakše et al., 2019). For all the participants, this was at, or better than, the current recommendation of 100 mg/dL. It is worth noting that the participant's LDL levels before the study began were not assessed, though, in Slovenia, where the study took place, the mean LDL level in 2018 was 140 mg/dL (NCD-RisC, 2021). It is rare to see an entire group of 154 people between 18 to 80 with optimal LDL levels.

It is important to note that not all the participants strictly followed the WFPB diet as recommended by Jakše et al., 2019. Some participants consumed fast food, sweet products, alcoholic drinks, vegetable fat, and some sweeteners, though in low quantities (mean: 6.5–0.2 g/day). Furthermore, some participants ate small amounts of food of animal origin (3–0.2 g/day for fish and meat; 0.1 g/day for milk and dairy products), though there was no consumption of eggs or added animal fat. Despite this, all the participants maintained optimal LDL levels. It is also worth noting that none of the participants were on any medications related to cardiovascular disease (in fact, none of the participants were on any medications except for 2 on thyroid medication, two on birth control, one taking medication for nausea, and 2 taking other medications). This contrasts with the previously mentioned distinction between Esselstyn et al., 2014 and Ornish et al., 1998, where removing egg whites, one cup per day of non-fat milk or yogurt, and oil reduced the chance of a reoccurring cardiac event by a factor of 22. Perhaps the distinction is that both Esselstyn et al., 2014 and Ornish et al., 1998 started with moderately to very sick patients while Jakše et al., 2019 started with healthy patients. This would suggest that if people were to adhere to a WFPB diet from a young age, before their arteries have suffered serious damage, the occasional (or minor) noncompliance wouldn't have any long-term effects. If a person's body is healthy, it can withstand and reverse small amounts of abuse. If, however, the abuse is constant and in large quantities, then the body won't be able to heal itself. These findings would suggest the need for more studies to be performed to figure out exactly how much 'small amounts of noncompliance' is.

Another Possible Approach to the Success of a WFPB Diet

As previously discussed, both the formation of atherosclerotic plaque from LDL and the inhibition of nitric oxide production is caused by oxidative agents. When the LDL gets oxidized, it can enter the subendothelial space, and it is oxidative stress that inhibits DDAH from degrading ADMA. If a person consumed foods with higher antioxidant levels, it would be reasonable to hypothesize that both these negative outcomes would be inhibited. In fact, if different food categories are analyzed based on their antioxidant content, the plant-based categories have significantly higher antioxidant levels. On the other hand, it is also possible that the antioxidant properties will be degraded during the digestive process and wouldn't affect antioxidant blood levels. A meta-analysis was done that studied the correlation between dietary intake of antioxidants and cardiovascular disease. It found a clear inverse relationship between antioxidant blood levels and cardiovascular disease. It also found a similar inverse relationship between fruit and vegetable consumption and cardiovascular disease. The higher levels of consumption of plant-based foods correlated with higher antioxidant levels. It is interesting to note that consuming antioxidant supplements did not correlate to an increase in antioxidant blood levels (Aune et al., 2018; (Aune, 2019). This would suggest that supplementation doesn't work, and more research needs to be done to discover why that is.

Conclusion

There is no question that a strict WFPB diet that restricts all added oil intake can be a lifesaver for someone who has already begun to exhibit symptoms of cardiovascular

disease. The necessity to follow the diet strictly, however, can be questioned in a healthy person. It is possible that as long as the majority of a healthy person's diet is WFPB, it would be enough. It is also possible that creating a high antioxidant diet (though not through supplementation) may have similar effects. Defining 'a healthy person' and 'mostly WFPB' would require future studies.

As an aside, although this research has focused on cardiovascular disease, many other illnesses such as diabetes, mental health, and cognitive decline have been shown to be less prevalent in people on a WFPB diet (Rajaram et al., 2019; Głąbska et al., 2020; Utami, Findyartini, 2018). Furthermore, a plant-based diet may have a greater impact on weight loss than other diets (Turner-McGrievy, et al., 2015).

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