

Continuing Education

Type 2 Diabetes and Weight Loss: Overview and Treatment Options

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Objectives:

- Name at least three etiologic factors in the development of type 2 diabetes.
- List two primary laboratory measurements for assessing the status of type 2 diabetes.
- Discuss the primary therapeutic options in the newly diagnosed patient with type 2 diabetes.
- Identify key elements for dietary and physical activity for patients with type 2 diabetes.

Diabetes: Overview of the Disease State Introduction

Diabetes is a term that primarily encompasses two major types of metabolic disorder: type 1 and type 2 diabetes mellitus (DM). Both types are characterized by high blood glucose and altered fat and protein metabolism. Patients who have type 1 DM are insulin deficient while those with type 2 DM have insulin resistance and β -cell dysfunction. Both types are associated with similar complications if left untreated or ill-managed. Type 2 DM makes up about 90% of all DM cases. In terms of clinical presentation, type 2 DM tends to develop later in life and more gradually compared with type 1 DM. Also, insulin therapy is often not needed until years after diagnosis of type 2 DM while it is immediately needed for type 1 diabetics.¹

As of 2012, almost 30 million Americans, or 9.3% of the population, were affected by DM. This number is continuing to rise as 1.4 million Americans are diagnosed with DM every year. There are almost 8 million estimated Americans with undiagnosed diabetes. DM was the 7th leading cause of death in 2010, though this may be underreported. Overall, this high prevalence of DM in the United States costs

over \$200 billion in healthcare costs. The average diabetic patient has 2.3 times the medical expenditures as an equivalent patient without DM.²

Risk factors for developing type 2 DM include age greater than 45, certain races and ethnicities (African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander), history of gestational diabetes, family history of diabetes, lack of physical activity, and a history of hypertension, dyslipidemia, or polycystic ovary syndrome (PCOS).^{1,3,4} Type 2 DM is believed to be caused by a combination of genetic susceptibility, obesity, and physical inactivity. Most patients with type 2 DM also present with abdominal obesity, which is a major contributor to insulin resistance.¹

Pathophysiology

Insulin is produced by the β -cells of the pancreas. In non-diabetic patients, the β -cells of the pancreas are able to adjust the amount of insulin they secrete to balance the plasma glucose levels based on insulin resistance. Normal blood glucose levels are thus maintained despite the intake, utilization, or production of glucose. However, in type 2 DM, patients have tissue resistance to the actions of insulin and a relative deficiency in insulin secretion. Individual patients may have more/less resistance or more/less β -cell deficiency compared to other patients.¹

In diabetic patients, the pancreas initially produces increased levels of insulin but over time the pancreas simply cannot keep up with the insulin resistance level to keep blood glucose at a normal level. In type 2 diabetic patients the insulin produced is inadequate to overcome the increased resistance and thus blood glucose rises. Impaired insulin action can cause an

increase in free fatty acid influx and triglyceride levels and a decrease in HDL cholesterol levels.¹

Diagnosis

Testing for DM should be done in all patients who are overweight and have at least one other risk factor for type 2 DM.^{1,5} Risk factors include those listed in the introduction such as physical inactivity, family history of type 2 DM, and personal history of gestational diabetes, among others.¹ Adults without risk factors should still be screened starting at age 45 years.^{1,5} If DM is not present, repeat testing should be done every 3 to 5 years.¹

There are four criteria that can be used to diagnose DM:

- 1) fasting plasma glucose (FPG) \geq 126 mg/dL (or \geq 7.0 mmol/L)
- 2) a 2-hour value from a 75 g oral glucose tolerance test (OGTT) \geq 200 mg/dL (or \geq 11.1 mmol/L)
- 3) casual plasma glucose level \geq 200 mg/dL (or \geq 11.1 mmol/L) with symptoms of diabetes
- 4) hemoglobin A_{1c} (HbA_{1c}) \geq 6.5%.

Two of the criteria must be met to confirm the diagnosis. If a patient has conflicting results from 2 different tests (i.e. elevated HbA_{1c} but normal FPG), then the test above the diagnostic cut off should be repeated.⁵ The diagnosis of DM should be confirmed through repeat testing if the patient has not been experiencing obvious hyperglycemia.^{1,5} A patient can be diagnosed with prediabetes if their test results are close but do not cross the diagnosis threshold.^{1,6}

Many patients with type 2 DM are asymptomatic but some do experience symptoms. These may include extreme thirst, frequent urination, increased hunger, blurry vision, tingling or numbness of the extremities, and wounds that don't heal.⁴ Furthermore, patients with type 2 DM who present with microvascular complications at

diagnosis likely have had hyperglycemia for years unknowingly. Microvascular complications include neuropathy, retinopathy, and nephropathy.¹

Prognosis and Complications

Diabetes is a lifelong disease with no cure. Death from any cause is reported to be 1.5 times greater in adults diagnosed with DM compared to those without DM.⁷ Unfortunately, it requires about 15 to 20 years of intensive glycemic control to lower the risk of macrovascular events and complications, such as atherosclerosis and coronary artery disease. However, excellent glycemic control from the time of diagnosis may contribute to a sustained reduction in microvascular and macrovascular risk.¹

There are many different potential consequences if DM is left untreated or inadequately treated. The American Diabetes Association (ADA) recommends screening for complications beginning at the time of diagnosis.^{1,5} One of these complications is a hyperosmolar hyperglycemic state (HHS) which is characterized by severe hyperglycemia, hyperosmolality, and dehydration without ketoacidosis.⁸ It is comparable to diabetic ketoacidosis (DKA), but HHS predominantly occurs in type 2 diabetics while DKA primarily occurs with type 1 diabetics.¹ HHS is the most serious acute, emergency complication of type 2 DM. The overall mortality rate for HHS is roughly 10 times higher than the mortality in patients with DKA.⁸

As many as 75% of diabetics die of a vascular complication, primarily coronary heart disease.⁹ Excess sugar due to DM can injure the walls of blood vessels that nourish the nerves, kidneys, and eyes, which can lead to neuropathy, nephropathy, and/or retinopathy, respectively.^{1,10,12} In order to help prevent these complications and catch them early in their progression, patients with

type 2 DM should have eye examinations every 1 to 2 years, screenings for nephropathy at least yearly, and screenings for neuropathy at least yearly.^{1,5} Furthermore, type 2 DM can also lead to atherosclerosis due to chronic inflammation and arterial wall injury.¹¹ Thus DM increases a patient's risk for developing cardiovascular disease.¹² While there has not been a high quality study that shows that improving glycemic control can decrease the risk of macrovascular disease events, there have been several studies that have demonstrated how modifying patients risk factors can help. This includes lowering blood pressure^{13,14} and managing lipid levels.¹⁵⁻¹⁷

Goals of Therapy

Per the American Diabetes Association 2016 guidelines, the glycemic recommendations for non-pregnant adults with DM are as follows:

Table 1: Glycemic Goals

Glycemic Goals	
HbA _{1c}	< 7.0%
Preprandial blood glucose	80-130 mg/dL
Postprandial blood glucose	< 180 mg/dL

Adapted from (Figure 8.1) American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017 Jan;40(Suppl.1):S1-S135. Available from: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf

More or less stringent glycemic goals may be appropriate depending on individual patient factors such as age, life expectancy, known cardiovascular disease (CVD) or advanced microvascular complications, and duration of DM. For example, a more stringent HbA_{1c} goal of < 6.5% may be appropriate for patients treated with metformin or lifestyle changes only, long-life expectancy, or a short duration of DM.

A less stringent HbA_{1c} goal of < 8.0% may be appropriate for patients with a history of severe hypoglycemia, advanced micro- or macrovascular complications, or extensive comorbid conditions.⁵

Self-monitored blood glucose (SMBG) is a tool that increases patient safety by detecting hypo- and hyperglycemia so that patients may treat themselves most appropriately.^{1,5} Frequency of SMBG may vary depending on each individual patient's medication regimen and their risk of hypoglycemia.^{1,5} It is also important to monitor blood glucose closely because glycemic control is vital to reduce DM complications.^{1,5,18} Patients who are on intensive insulin regimens (e.g. multiple doses per day or insulin pump therapy) should use SMBG throughout the day before meals and snacks, at bedtime, prior to exercise, when they suspect hypoglycemia, and occasionally postprandially.⁵ For patients on basal insulin or oral agents only, there is insufficient evidence to determine if SMBG should be recommended and how often testing should be done.^{5,19,20} SMBG may be helpful though as increased testing frequency has been associated with meeting HbA_{1c} targets.²¹

Prevention

Patients who are at an increased risk (prediabetes) for the development of type 2 DM can be treated in order to prevent or delay the disease. Those who are at a high risk for type 2 DM, including people with HbA_{1c} 5.7-6.4%, impaired glucose tolerance, or impaired fasting glucose are the best candidates for prevention. Lifestyle modifications and pharmacologic interventions are available for treating patients with prediabetes, and diabetes self-management education and support provides a way for these patients to gain the tools necessary to prevent or delay the development of DM. All prediabetes

patients should also be screened for cardiovascular disease, which can be prevented by controlling modifiable risk factors such as hypertension and dyslipidemia.⁵

For pharmacological treatment of prediabetes, metformin should be considered. Metformin is especially useful in those with a BMI ≥ 35 kg/m², less than sixty years old, women with previous gestational diabetes, and/or those whose HbA_{1c} has risen despite lifestyle modifications. While other agents have been shown to decrease the incidence of DM in patients with prediabetes, metformin has the strongest evidence base as well as long-term safety for pharmacologic treatment.²² Other agents that have been shown to reduce the occurrence of DM in persons with prediabetes are alpha-glucosidase inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones. The Diabetes Prevention Program Outcomes Study (DPPOS) showed that metformin was less effective than lifestyle modification but may be cost-saving over a ten-year period.²³ Metformin was shown to be as effective as lifestyle changes in persons with BMI ≥ 35 kg/m², but the results were less significant for patients who were greater than sixty years old.⁴ For women with a history of gestational diabetes mellitus, the DPPOS revealed that metformin and intensive lifestyle modification resulted in a 50% reduction for the development of DM, and both of these treatments were still effective after a ten-year follow-up.^{25,26}

Pharmacologic Treatment of Diabetes

The initial agent of choice for pharmacologic therapy in type 2 DM is metformin as long as there is no contraindication to its use and the patient has no problems with tolerability. This is supported by the findings of a meta-analysis published by The Journal of the American

Medical Association (JAMA).²⁷ For newly diagnosed patients who are symptomatic and/or have HbA_{1c} $\geq 10\%$ and/or blood glucose levels ≥ 300 mg/dL, insulin therapy should be considered because metformin alone will likely not be enough for these patients.¹ Metformin is a great option for many patients though because it is safe, effective, inexpensive, and may reduce the risk of cardiovascular events and death.²⁸

While it is a safe option, there are limiting factors. Metformin should only be used in patients with an eGFR ≥ 30 mL/min/1.73 m².²⁹ Metformin should be discontinued when patients experience nausea, vomiting, or dehydration, and vitamin B12 levels should be monitored periodically (especially in patients with anemia or peripheral neuropathy) based on the findings from DPPOS which found metformin to be associated with vitamin B12 deficiency.^{5,30} Patients who have a contraindication or intolerance to metformin should be placed on a drug from a different class.

When the HbA_{1c} reaches 9% or more or the patient's HbA_{1c} target is not met after three months while on monotherapy, dual combination therapy should be considered. Generally, dual combination therapy is metformin plus another agent from a different drug class (i.e. metformin + sulfonylurea). A recent meta-analysis suggested that each additional noninsulin agent added to initial therapy lowers HbA_{1c} approximately 0.9-1.1%.³¹ If a patient's HbA_{1c} goal is not met after three months of dual combination therapy, consider triple combination therapy. If HbA_{1c} target is not achieved after three months on triple therapy and the patient is taking an oral combination, move to a basal insulin or GLP-1 RA. If the patient's triple therapy included a GLP-1 RA, add basal insulin. If the triple therapy included an optimally titrated basal insulin, add a GLP-1 RA or

mealtime insulin. Metformin should be maintained if the patient has been using it as part of his or her regimen, and the other oral agents can be discontinued to avoid complex or costly treatment. It is important to note that when beginning any combination therapy, the drug selection should be based

on patient and disease-specific factors.⁵ These options are summarized in Table 3.

Table 2 is adapted from the ADA Standards of Medical Care in Diabetes, displays the potential risks and benefits associated within each drug class.

Table 2: Antidiabetic Drug Classes: Risks and Benefits

Drug Class	Efficacy	Hypoglycemia Risk	Weight Effects	Adverse Drug Effects	Cost
Metformin	High	Low	Neutral/loss	GI/lactic acidosis	Low
Sulfonylurea	High	Moderate	Gain	Hypoglycemia	Low
Thiazolidinedione	High	Low	Gain	Edema, HF, fractures	Low
DPP-4 Inhibitors	Intermediate	Low	Neutral	Rare	High
SGLT2 Inhibitors	Intermediate	Low	Loss	GU, dehydration, fractures	High
GLP-1 Receptor Agonists	High	Low	Loss	GI	High
Insulin (basal)	Highest	High	Gain	Hypoglycemia	High

DPP-4: Dipeptidyl peptidase-4, SGLT2: sodium-glucose co-transporter-2, GLP-1: Glucagon-like peptide-1, HF: heart failure, GI: gastrointestinal, GU: genitourinary

Adapted from (Figure 8.1) American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017 Jan;40(Suppl.1):S1–S135. Available from: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf

Pharmacologic Treatment Summary

Pharmacologic therapy for type 2 DM is a step-wise process dictated by several factors, including patient preferences, side effect profile, cost, efficacy, and clinician experience. Each step up in therapy involves the addition of one agent, and metformin is the initial agent of choice for step 1 (monotherapy) based on its efficacy, safety,

low cost, and potential to reduce cardiovascular events. Once a patient is on triple oral combination therapy, the agents used tend to favor the injectable agents such as basal insulin and GLP-1 RA, especially if triple oral therapy is not controlling a patient's HbA_{1c}. Efficacy across the agents available is very similar, and basal insulin therapy has the highest efficacy.^{1,5}

Table 3: Steps of Diabetes Therapy

Step 1:	Healthy eating, weight control, increased physical activity, and diabetes education
Step 2:	Metformin alone
Step 3: if HbA_{1c} target is not met after 3 months of monotherapy	Continue metformin → add sulfonylurea
	Continue metformin → add thiazolidinedione (TZD)
	Continue metformin → add DPP-4 inhibitor
	Continue metformin → add SGLT2 inhibitor
	Continue metformin → add GLP-1 RA
	Continue metformin → add basal insulin
Step 4: if HbA_{1c} target is not met after 3 months of dual therapy	If metformin + sulfonylurea → add TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin
	If metformin + thiazolidinedione → add sulfonylurea, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin
	If metformin + DPP-4 inhibitor → add sulfonylurea, TZD, SGLT2 inhibitor, or basal insulin
	If metformin + SGLT2 inhibitor → add sulfonylurea, TZD, DPP-4 inhibitor, or basal insulin
	If metformin + GLP-1 RA → add sulfonylurea, TZD, or basal insulin
	If metformin + basal insulin → add TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 RA
Step 5: if HbA_{1c} target is not met after 3 months of triple therapy	Change to metformin + basal insulin + mealtime (bolus) insulin
	Change to metformin + basal insulin + GLP-1 RA

Adapted from (Figure 2) American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017 Jan;40(Suppl.1):S1–S135. Available from: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf

Lifestyle Changes: Nutrition and Weight Management

Lifestyle changes are recommended for most individuals to promote better health outcomes. For patients who are at a high risk for DM or who have been diagnosed with DM, nutrition and exercise changes to promote weight management can help reduce their risk for cardiovascular events. The Diabetes Prevention Program (DPP) was a multicenter, randomized clinical trial with about 1000 participants designed to prove that with lifestyle modifications, individuals at high risk for type 2 DM could reduce their risk of developing diabetes. After 3 years of lifestyle interventions, including calorie counting and exercise, the DPP showed a 58% reduction in incidence rate of diabetes.³² This study shows how

lifestyle modifications can significantly reduce the risk of type 2 DM in individuals.

Lifestyle management is a key factor in the overall management of type 2 DM. There is strong evidence to support lifestyle modifications for those with DM who are overweight or obese to improve glycemic control and reduce the need for medications with type 2 DM. Some studies have shown a reduction in HbA_{1c} values as well as fasting glucose with low calorie diets in obese patients with type 2 DM. Overweight and obese individuals with DM who are ready to achieve weight loss should have a goal of at least 5% weight loss through lifestyle changes.⁵ The Look AHEAD trial was a multicenter, randomized clinical trial that demonstrated a 5-10% weight loss in diabetic patients was associated with

improvements in blood sugar levels, blood pressure, triglycerides, and HDL cholesterol. The study found that the greater the weight loss the individual achieved, the greater the reduction in overall risks.³³ Some of the aspects in lifestyle management that individuals can implement include, the diabetes self-management education (DSME), nutrition therapy as well as physical activity.⁵

The DSME programs are meant to help patients with DM gain the knowledge and skills needed for optimal care of diabetes. There are four critical time frames where the need for DSME programs should be evaluated by a medical care provider to ensure the patient is informed and able to manage their DM. These include: at diagnosis of diabetes, annually for education assessment, when new complicating factors arise, or when transitions in care occur. DSME focuses on a patient-centered approach to caring for their DM while providing them the tools they need to make self-management decisions. Studies have shown that DSME has improved diabetes knowledge and self-care behaviors as well as reducing healthcare costs.⁵

Nutrition Recommendations

For most diabetic patients, nutrition therapy can be very challenging to plan and maintain. There is not one diet for all diabetic patients, but there are recommended guidelines to follow where small adjustments can be made to fit each person's needs. All individuals are recommended to receive medical nutrition therapy (MNT), preferably by a registered dietician who can help make knowledgeable decisions as to what works best for that person. Diabetic patients are recommended to follow a diet that contains nutrient dense, high quality foods such as the Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet.⁵ There is also the Idaho Plate

Method available for patients that is helpful to control meal portions.

Overall nutrition recommendations for diabetic patients include watching the amount of carbohydrates consumed, as this is the biggest influence in post-meal blood glucose level. When choosing carbohydrates, patients should choose nutrient-dense, high fiber foods instead of processed foods that could have added sodium, fat and sugars. Unsaturated fat containing foods should be incorporated in their diet instead of foods containing trans or saturated fat. When selecting the meat for their diet, a leaner protein source is preferred. Finally, sodium intake should generally be limited to no more than 2,300 mg per day for individuals.³⁴

The Mediterranean Diet reduces the risk of heart disease, and is associated with a lower LDL cholesterol build up in the arteries. Some of the key components of this diet are eating primarily plant based foods, including fruits, vegetables, whole grains and nuts. It also encourages eating fish and poultry at least twice a week, and limiting red meats to no more than a few times a month. This diet also recommends using olive or canola oil instead of butter, and herbs or spices instead of salt. The focus of this diet is not to limit total fat consumption, but to make healthier choices about the fats consumed.³⁵

The Dietary Approaches to Stop Hypertension, also known as the DASH diet, is designed to encourage healthy eating to help treat or prevent high blood pressure. This diet focuses on reducing the amount of sodium consumed as well as encouraging foods that are rich in nutrients that can lower blood pressure, such as potassium, calcium, and magnesium. There are two recommendations from the DASH diet, one is the standard diet where 2,300 mg of sodium can be consumed a day, whereas the second is a low sodium diet with only 1,500

mg of sodium per day. The American Heart Association recommends 1,500 mg of sodium a day as a limit, but patients should always talk with their physician to see what is best for them. Despite the differences in sodium, the diets are relatively the same, encouraging whole grains, fruits, vegetables, and low-fat dairy products. Patients following the DASH diet are recommended to consume 6-8 servings of grains a day, where one serving equals one slice of whole-wheat bread, one ounce dry cereal, or half of a cup of cooked cereal, rice or pasta. Vegetables should be consumed in 4-5 servings per day, examples include one cup of raw leafy greens or half of a cup of cut-up raw or cooked vegetables. This diet also includes 4-5 servings of fruit a day, including half of a cup of fresh, frozen or canned fruit, or four ounces of juice. Dairy should be consumed in only 2-3 servings a day, where one serving includes one cup of skim or 1% milk, or one cup of low fat yogurt. Lean meats, poultry and fish should consist of 6 servings or fewer a day, and nuts, seeds or legumes should only be 4-5 servings a week. This diet also limits the use of fats or oils to 2-3 servings per day, and sweets to only 5 servings or fewer a week.³⁶

Both diets are similar in the types of foods consumed, and both promote healthy eating habits for patients with DM. It is ultimately up to the individual as to which diet to follow based on what works best for them. The DASH diet has more specifics outlined in the number of servings, which may be easier for some patients to plan. However, the Mediterranean diet focuses not on a set criteria of servings for the diet, but more so on the healthy choice alternatives to everyday items.³⁷

The Idaho Plate Method is a way for patients to control the portions of their food when following a healthy diet. It consists of dividing a nine-inch plate in half, and using one half of the plate solely for vegetables for

that meal. The other half of the plate is divided into quarters, where one quarter contains protein and the other quarter contains starches, starchy vegetables, grains, or bread. Starchy vegetables can include corn, peas, potatoes and squash. This method also includes a small bowl on the side for a small serving of fruit, as well as an eight-ounce cup for milk or yogurt. Food on the plate is not to be piled higher than half of an inch on the plate to ensure adequate portions.³⁸ This method is a good resource for patients to use to ensure they are following healthy habits and portion control with their diet.

Exercise Recommendations

Physical activity and exercise are just as important as nutrition for individuals with type 2 DM. Physical activity includes any movement that increases energy use; whereas exercise is considered a more specific form of physical activity designed to improve physical fitness. Exercise has been shown to have several benefits including: improved blood glucose control, reduced cardiovascular risk, increased energy as well as burning extra calories and fat to help manage weight and improve well-being. Exercise interventions of at least eight weeks also has shown to lower HbA_{1c} in those with type 2 DM.⁵ Overall, implementing physical activity can lead to improvements in overall health, especially in patients with type 2 DM.

Physical activity for diabetics is beneficial if done at a standard frequency and type of activity. It is recommended that adults over age 18 perform 150 minutes per week of moderate-intensity activity or 75 minutes per week of vigorous-intensity activity, or an equivalent combination of the two. Moderate-intensity activity include walking at a moderate or brisk pace or stationary bicycling; whereas vigorous-intensity includes jogging, running, or

bicycling at more than 10 mph.³⁹ It is also recommended that adults do muscle-strengthening exercises at least two days of the week. Those who are over age 65 or are unable to perform at this frequency of activity, should be as physically active as they are able. Individuals are also encouraged to reduce the amount of time spent sedentary at a computer or watching TV. Instead, try to limit the sedentary activity by standing or taking a short walk as often as possible.⁵

In summary, lifestyle modifications are an important component of the overall management of type 2 DM. These changes are associated with reduced risk of cardiovascular disease, improved glycemic control, and potential improvement in certain laboratory values such as HbA_{1c} and lipid levels. A 5% reduction in weight loss can significantly lessen the risks associated with type 2 DM. Lifestyle modifications are

a great way to improve health outcomes, and should be recommended to all patients with DM.

Conclusion

Type 2 DM is a very common metabolic disorder characterized by high blood glucose and altered fat and protein metabolism. To treat DM, metformin is the preferred primary treatment, and the next agent should be chosen based on the patient's preference. There is also no specific diet that is recommended for all diabetic patients; individuals should discuss with their physician and a dietician to see what diet will best suit their needs for health and weight loss. With step-up guided pharmacologic therapy along with lifestyle modifications, diabetes is manageable to all individuals. Exercise should be encouraged in all patients that are capable.

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