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Review Article

Consensus statement for the management of dyslipidemia and hypertension in the Indian population with diabetes

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ABSTRACT

The mortality rate from cardiovascular disease (CVD) in India is higher than the global figures (272 per 100,000 persons vs. 235 per 100,000 persons, respectively). Smoking, obesity, hypertension, diabetes and dyslipidemia are the known risk factors for atherosclerotic cardiovascular disease (ASCVD). The treatment of either condition aims to reduce the risk of ASCVD. This goal is achievable only when a holistic, simultaneous treatment is initiated and is monitored to reduce the blood glucose, blood cholesterol, and BP. India heralds a huge population of nearly 73 million people with diabetes. Diabetes is one of the major contributors of ASCVD, dyslipidemia and hypertension often coexist with diabetes. Patients diagnosed with either condition need risk stratification, followed by defining the treatment target for each risk category and developing appropriate treatment strategies based on the risk category. Unfortunately, there is no clear guideline that defines the treatment targets and subsequent management. This statement has been created based on the vast experience and an extensive literature review conducted by experts from multidisciplinary teams to address several treatment dilemmas that are routinely faced by clinicians when treating their patients with diabetes. An attempt is made to provide well-defined answers to these quandaries. This statement discusses screening, diagnosis, risk stratification, treatment targets, and management of dyslipidemia and/or hypertension in patients with diabetes and provides a roadmap for the treatment of Indian patients to curtail the risk of ASCVD.

Keywords: Cardiovascular disease, Diabetes, Dyslipidaemia, Hypertension, Risk assessment, Target organ damage

INTRODUCTION

Diabetes mellitus (DM) is a chronic condition characterized by hyperglycemia and is associated with other metabolic disorders. It occurs due to the decreased secretion of the insulin hormone by the pancreas (type 1 DM (T1DM)), the inefficient utilization of insulin by the peripheral tissues (type 2 DM (T2DM)) or a combination of these two mechanisms.[1]

The past 20 years have seen a rapid and unprecedented increase in the prevalence of DM and associated

metabolic disorders globally, especially in countries like India, China and the United States (Table 1).[2]

The endemic proportions of DM pose a significant burden on the Indian public health care economics for the prevention, detection, management, and treatment of the condition. As per the International Diabetes Federation (IDF) 2017 statistics, approximately one in 11 adults worldwide has diabetes (425 million), and more than 72 million of those 425 million adults are from India.[2] By 2030, diabetes is expected to affect 79.4 million people in India.[3] This number is expected to increase by 100% in 2045. The rise in diabetes cases at this alarming rate in the Indian population is attributed mainly to rapid urbanization, modernization, lifestyle and dietary changes and hereditary/genetic factors.[2,4]

Table 1: Diabetes prevalence and projection in top three countries.

Rank	Country/territory	2017	2045
		Number of people with diabetes	Number of people with diabetes
1	China	114.4 (104.1-146.3)	134.3 (103.4-165.2)
2	India	72.9 (55.5-90.2)	119.8 (86.3-149.7)
3	United States	30.2 (28.8-31.8)	35.6 (33.9-37.9)

The prevalence of hypertension was found to be higher in men, whereas the presence of dyslipidemia was predominant in women. A study by Yadav D et al, emphasized that the severity of diabetes correlated with the duration of the disease and the age of the patient.[5]

The clinical symptoms of diabetes include polyuria, polydipsia, polyphagia, blurred vision and yeast infections.[2]

One of the major challenges in the treatment and management of DM is the presence of several comorbidities. These include obesity, dyslipidemia, microvascular complications (retinopathy, nephropathy, and neuropathy), chronic kidney disease (CKD) and macrovascular diseases (CVD, hypertension, stroke, and foot complications). The comorbidities associated with DM significantly affect the quality of life and increase the mortality rates.[6]

The long-term consequences and mortality are due to microvascular and macrovascular complications.[2,4]

Dyslipidemia is marked by an abnormality in the lipid profile, i.e., in the levels of triglycerides, HDL-C, and LDL-C. These changes are affected by alterations in the lipid metabolic enzymes due to insulin resistance.[7] Interestingly, these lipid compositions are more atherogenic in individuals with diabetes, thus aggravating the progression to atherosclerosis.[8,9]

The risk of hypertension is double in people with diabetes than in those who do not have diabetes. It has been estimated that 60% of people with diabetes have hypertension also.[10,11] The co-existence of hypertension and DM significantly increases the risk and incidence of CVD, heart failure, stroke and microvascular conditions, such as retinopathy and nephropathy. Thus, it is essential and beneficial to manage hypertension in people with diabetes.[12] The link between hypertension and diabetes is complex and is thought to be promoted by the adrenergic system, primarily the renin–angiotensin–aldosterone system. Additionally, it has been suggested that the calcium-calmodulin pathway plays a role in both these conditions. The defects in the calcium-calmodulin signaling pathway result in an increased retention of calcium in the pancreatic beta cells, thus inhibiting the expression of the insulin gene.[13] Overall, insulin resistance and obesity play a critical role in the development of diabetes-associated dyslipidemia and hypertension. Together, these conditions fall under the umbrella of metabolic syndrome, which is reaching widespread proportions in India. Thus, there is an overarching need for the effective management and treatment of not only diabetes but also the comorbidities associated with it.

Management of the diabetes spectrum requires the simultaneous use of several therapeutics designed to reduce blood glucose levels and comorbidities and complications associated with DM. An all-inclusive, patient-centric approach for therapies is the need of the hour.

Rationale for the development of the consensus statement

There is a lack of clear guidelines regarding the management of diabetes-associated comorbidities, like hypertension and dyslipidemia, for the Indian population. The high prevalence and burgeoning incidence bring to fore the urgent need for a focus on defining newer management protocols that can cater to these high-risk populations.

This document aimed to develop a framework for clinicians and health care providers for the effective management and ultimately, successful clinical outcomes

in people with diabetes in the context of other comorbidities, such as dyslipidemia and hypertension.

REVIEW OF LITERATURE

Understanding of clinical pathophysiology

Several epidemiological studies suggested a strong correlation between hyperglycemia and increased incidence of CVD. Both T1DM and T2DM are associated with an increased incidence of ASCVD. Every 1% increase in HbA1c is associated with about 11%-16% increase in the incidence of cardiovascular conditions. Nearly 97% of the patients with diabetes have dyslipidemia and 40%- 80% of the patients with diabetes have hypertension based on the definition of hypertension that has been utilized.[14,15]

The evidence garnered from human studies and animal models has shown that the molecular and clinical pathology of how hyperglycemia and insulin resistance contribute to ASCVD is complex and involves several mechanisms.[16]

Atherosclerosis is defined as fatty degeneration and vessel stiffening and it affects medium and large-sized arteries. In this process, the sub-intima of the artery undergoes thickening, which then invades the arterial lumen. In the early stages, the lesion appears as a fatty streak (made up of fat-laden macrophages called foam cells), which later progresses to a fibrous plaque, a key feature of atherosclerosis. Further progression results in a large amount of lipid accumulation in the lesion, which becomes unstable, ruptures, and causes thrombotic occlusion of the artery.[17] This manifest as a clinical event.

Dyslipidemia is strongly associated with ASCVD. In total, 79% of Indians with diabetes have an abnormal lipid profile compared with 97% of the Americans with diabetes and an abnormal lipid profile.[14,17] In addition, patients with diabetes, specifically those from the Indian subcontinent, have increased levels of atherogenic small LDL-C particles that are more susceptible to oxidation, high triglyceride levels, and low HDL-C levels.[17,18] The oxidized LDL-C initiates several proatherogenic events, such as attracting leukocytes, improving the capacity of macrophages to ingest lipids (formation of foam cells), and stimulating the proliferation of leukocytes, endothelial cells and smooth muscle cells. All these steps eventually result in the formation of atherosclerotic plaques. Patients with diabetes also present with glycated LDL-C and HDL-C, this condition, in turn, increases the stability of LDL-C and reduces the stability of HDL-C. Insulin enhances the activity of lipoprotein lipase, which increases the fatty acid uptake and suppresses the release of free fatty acids. Insulin resistance seen in T2DM potentially results in hypertriglyceridemia.[16]

Nearly half of the patients with diabetes have hypertension, which is another major driver of the ASCVD risk in these patients. Several studies have demonstrated a two-fold higher risk of CV events and death in people with diabetes and hypertension than in those with normal BP values. Furthermore, the evidence shows that lower BP is associated with lower CV events and there are established benefits associated with a reduction in BP.[19]

In summary, hyperglycemia and insulin resistance promote atherogenesis by affecting oxidation and glycation of lipoproteins and by increasing the triglyceride levels. Hyperglycemia is known to increase the expression of various cell adhesion molecules in the endothelial cells, which is mediated through the activation of protein kinase C (PKC), NF-κB pathways, and increased oxidative stress caused by hyperglycemia and insulin resistance (Figure 1).[18,20]

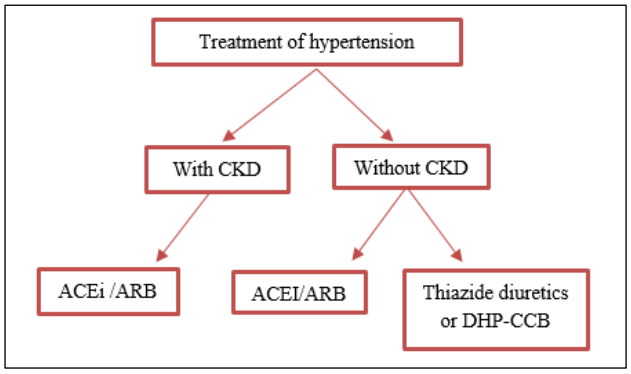

Figure 1: Antihypertensive treatment options for patients with diabetes with/without CKD.

Thus, the endothelial cells in atherosclerosis-susceptible regions have a high proliferation rate and adhesion of leukocytes, thereby contributing to plaque formation. Endothelial proliferation and apoptosis play an important role in the stability of an atherosclerotic plaque.

A microarray analysis of gene expression, followed by a pathway enrichment analysis and quantitative PCR validation, found that telmisartan modulates the expression of key genes responsible for cell cycle progression and apoptosis.[21]

In addition to its known anti-inflammatory and antioxidant effects on the endothelium, telmisartan promotes endothelial cell quiescence and survival.[21] Also, atherosclerosis associated with obesity and diabetes has been known to be a low-grade chronic inflammation that increases the risk of ASCVD.[16] This findings may have important implications for the anti-atherogenic and plaque-stabilizing roles in addition to BP control in patients with hyperglycemia and insulin resistance.[21]

Identification of risk factors

Indians develop ASCVD at a younger age than other populations do. Dyslipidemia, hypertension,

inflammation and obesity accelerate the development of atherosclerosis when they are associated with diabetes.[22] The primary risk factors for the development of diabetes are age, family history, smoking, and a lack of physical activity.[2] The primary risk factor for obesity and diabetes is an increased intake of high-calorie foods that are poor in fiber content, those with a low overall nutritive value, those with low glycemic index components and those which are rich in saturated fats and trans fats from animal sources.

Exercise increases metabolism, reduces insulin resistance, enhances glucose uptake, and lowers fatty acid metabolites that promote insulin resistance. Thus, a lack of physical activity is a critical risk factor for diabetes.[23] These risk factors result in inflammation, endoplasmic reticulum (ER) stress and release of adipokines and lipokines, which further promote insulin resistance that ultimately leads to hyperglycemia.

Indians have the highest levels of insulin resistance among the Asian and South Asian populations due to the abnormal abdominal fat distribution and inflammation. Family history is one of the major independent risk factors for diabetes.[21]

Two independent genome-wide association studies in Indians have found that the PPARG, KCNJ11, TCF7L2, SLC30A8, HHEX, CDKN2A, IGF2BP2 and CDKAL1 genes are associated with diabetes.[21] Babies of mothers with gestational diabetes and diabetes are more prone to developing diabetes in their later life, independent of maternal genetics.[22]

Some of the risk factors can be mitigated by creating awareness in the population via promoting healthy dietary habits, encouraging physical activity, making an early diagnosis and offering an appropriate intervention.[23]

Risk stratification

The key focus of the public health system should be early-stage intervention and prevention programs by creating awareness for modifications in the lifestyle and dietary habits.

The oldest and most well-established risk stratification system designed for the Caucasian population is the Framingham Risk Score (FRS) (Box 1), which identifies the population and people who are at high risk of developing CVD within a 10-year period.[24,25]

Table 2: Important ASCVD risk assessment tools-Framingham, MESA, UKPDS, and JBS-3.

Box 1: Framingham risk assessment tool	Box 2: MESA risk calculator	Box 3: UKPDS tool calculator for people with T2DM	Box 4: JBS-3
Age	Age	Age	Age
Sex	Sex	Sex	Sex
Total cholesterol	Ethnicity/race	Height	Ethnic group
HDL-C	Coronary artery calcification	Weight	Height
Systolic BP	Diabetes	Total cholesterol	Weight
Antihypertensive therapy	Smoking status	HDL-C	Total cholesterol
	Family history of myocardial infarction	Smoking status	HDL-C
	Total cholesterol	Systolic BP	Family history of comorbidities
	HDL-C		
	Systolic BP		
	Antihypertensive therapy		
	Lipid lowering therapy		

Several risk scores, such as the Multi-Ethnic Study of Atherosclerosis (MESA) risk calculator (Box 2), Reynolds score and United Kingdom Prospective Diabetes Study (UKPDS) tool (Box 3) are now available for risk calculation.[25-27]

The MESA tool includes an essential parameter, i.e., calcium scoring of coronary arteries. The tool also includes age, sex, ethnicity, diabetes, smoking status, family history, total cholesterol, and HDL-C. Indians have the onset of ischemic disease almost a decade before and develop diabetes often much earlier than the Western population does. As the emphasis is more on the age when the risk is calculated, the risk is underestimated for the Indian population.[26]

The current prevention strategies of the Joint British Societies (JBS3) tend to focus on the 10-year relative risk

in a patient. Basically, it includes the lifetime risk of CVD events, JBS-3 score assesses the life-time or 30-year risk score of patients.

Also, Indian ethnicity is specifically represented in JBS3 and it provides a more accurate estimation of the cardiovascular risk in Indian patients (Box 4).[28]

Dyslipidemia: diagnosis, screening and treatment targets

It is well established that the detection of abnormal lipid profiles at an earlier stage and administration of an appropriate treatment can reduce the risk of cardiovascular complications in patients with diabetes. Thus, consequent treatment of dyslipidemia and glycemic control is imperative.

A study conducted by Laakso M et al, provides evidence that low HDL-C and HDL2-cholesterol, high VLDL-C and high total and VLDL triglycerides are all strong risk indicators of coronary heart events in patients with diabetes.[27]

Table 3 describes the risk factors involved and the targets to be achieved.[25]

Table 3: Risk factors involved and targets.

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL	<55	<80	<70
	Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH			
	History of premature ASCVD (<55 male, <65 female)			
Very high risk	Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%	<70	<100	<80
	DM or stage 3 or 4 CKD with 1 or more risk factor(s)			
	HeFH			
High risk	≥2 risk factors and 10-year risk 10%-20%	<100	<130	<90
	DM or stage 3 or 4 CKD with no other risk factors			
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS- acute coronary syndrome, apo, apolipoprotein, ASCVD- atherosclerotic cardiovascular disease, CKD- chronic kidney disease, DM- diabetes mellitus, HeFH- heterozygous familial hypercholesterolemia, HDL-C- high-density lipoprotein cholesterol, LDL-C- low-density lipoprotein cholesterol, NR- not recommended.

Apolipoprotein B comprises the major fraction of protein content in LDL-C and each particle contains only one Apo B. Subsequently, Apo B measurements reflect the number of particles, in contrast to LDL-C that measures the amount of cholesterol in LDL-C particles.[30] Apolipoprotein A1 (Apo A1) is the main lipoprotein present in HDL-C. Hence, the Apo B/Apo A1 ratio may be a better risk predictor of atherosclerotic disease than the LDL/HDL ratio.[30]

Hypertension: diagnosis, screening and treatment targets

Being a strong comorbidity, hypertension demands regular and strict monitoring to achieve better control over hyperglycemia. Ambulatory BP monitoring (ABPM) is used to obtain out of office BP readings at set intervals, usually over a period of 24 hours. Home BP monitoring (HBPM) is used to obtain a record of out-of-office BP readings taken by a patient. Both methods typically provide BP estimates that are based on multiple time measurement. A systematic review conducted by the US Preventive Services Task Force reported that ABPM is superior in predicting long-term CVD outcomes than office BP.[31]

To achieve good compliance with antihypertensive agents, it is recommended to record BP at home. For ruling out masked hypertension or white-coat hypertension, ABPM is recommended. Ambulatory and home BP readings are crucial tools for confirming the diagnosis of hypertension, especially in the younger population and in patients newly diagnosed with hypertension. Among people with diabetes, HBPM/ABPM assists in checking for the nocturnal dip in BP. Patients with absent nocturnal BP dip are at an increased risk of ASCVD.[32]

Guidelines generally recommend that patients be stratified according to the risk factors involved. Hence,

patients should undergo CHD (coronary heart disease) risk assessment initially to guide the intensity of preventive treatment. There are different risk assessment criteria. Ankle brachial index (ABI), coronary calcium score and carotid intima-media thickness are useful tools in predicting the risk of CVD in the Indian population.[33]

Ankle brachial index is a noninvasive method to measure the peripheral vascular resistance and to determine the mortality risk. Low ABI <0.9 confirms atherosclerosis.[34]

Ultrasound CT is a well-established tool to detect and quantify coronary artery calcium. Coronary artery calcium cut-off values at which intermediate-risk patients were reclassified to the high- and low-risk category were 615 and 50 Agatston units, respectively.[35]

Similarly, ultrasound can be used to monitor the intima-media thickness of the carotid arteries. The carotid intima-media thickness values ≥75th percentile is considered high and are indicative of an increased CVD risk. Values between the 25th and 75th percentiles are considered average and are indicative of an unchanged CVD risk. Values ≤25th percentile indicate a lowered CVD risk.[36]

In patients with a high coronary artery calcium score, if the carotid intima-media thickness value is high, aggressive high statin therapy is recommended.

The levels of TNF-alpha are also related to concomitant kidney dysfunction.[40] Studies have found that atorvastatin attenuates TNF-alpha production.[37] C-reactive protein is only a surrogate marker, whereas TNF-alpha is an inflammatory mediator. The American Diabetes Association (ADA) 2018, JNC 7 and Systolic Blood Pressure Intervention Trial recommend the BP targets of ≤130/80 mmHg for adults with diabetes or CKD.[32]

Treatment strategies

Diet control and lifestyle modifications are the first step in the management of the lifestyle disorders, which form the components of metabolic syndrome. In addition, effective pharmacotherapy is necessary for aggressive control of diabetes and its comorbidities. Treatment for glycemic control is beyond the scope of this document. Management of dyslipidemia and hypertension in diabetes with/without end-organ damage is discussed here.

DISCUSSION

Dyslipidemia management in diabetes

Statins or HMG-CoA reductase inhibitors are universally acceptable treatment options for the primary and secondary prevention of CVD. Fibrates lower the plasma triglyceride levels. When lifestyle-related modifications cannot achieve the target levels, fibrates are used to treat severe hypertriglyceridemia in patients with diabetes.[25]

The use of statins is recommended in every patient with diabetes. The LDL-C level is lowered by 30%-50% and by ≥50% with a moderate-intensity and a high-intensity statin therapy, respectively.[25] Recommendations for statin therapy in patients with diabetes based on their ASCVD risk are described in Table 4.[38]

Table 4: ADA 2018 guideline recommendations for statin therapy in patients with diabetes.

Condition	Recommendations
Diabetes and ASCVD	High intensity statin + lifestyle therapy
Diabetes and ASCVD risk factor	Moderate intensity statin + lifestyle
Diabetes without ASCVD	
Diabetes and ASCVD + LDL cholesterol ≥70 mg/dL despite maximum tolerated statin dose	Consider additional LDL lowering therapy (PCSK9 inhibitor/ezetimibe)

Table 5: ACC/AHA guideline recommendations for statin use.

	Age (years)	10-years ASCVD risk	Treatment
Primary prevention (all LDL-C in mg/dl, with a 10-year ASCVD event risk)	40-75	>5% but <7.5%	Lifestyle changes + moderate intensity statin
		≥ 7.5%	Lifestyle changes + moderate or high intensity statin
Secondary prevention (Patients with clinical ASCVD)	≤75		High intensity statin
	>75		Moderate intensity statin (contraindications or safety concerns should be addressed)

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology guidelines recommend that adults aged ≥21 years be treated with statins if LDL-C ≥190 mg/dL.[25]

Further treatment thresholds to initiate the treatment based on the age and ASCVD risk and the intensity of treatment recommended are given in Table 5.[39]

There is a suggested similarity in the pathophysiology of atherosclerosis and glomerulosclerosis, the progression of kidney disease has been studied in patients with hyperlipidemia. In patients with CKD, atorvastatin at a moderate dose is preferred over rosuvastatin, as atorvastatin has fewer detrimental effects on renal function, especially in patients with diabetes. Atorvastatin has been found to preserve the glomerular filtration rate (GFR) in patients with diabetes.[39]

Management of hypertension in patients with diabetes

First-line oral antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium channel blockers, and angiotensin receptor blockers (ARBs), are useful. Furthermore, in patients with dyslipidemia, ACE inhibitors and ARBs are preferred over beta-blockers.

The ACE inhibitors are still recommended as the first-line therapy. However, due to bradykinin-induced cough and allergic complications that lead to noncompliance, ARBs are preferred as the first-line therapy by many. Furthermore, newer ARBs, particularly azilsartan and telmisartan, act for longer than 24 hours.[32] Telmisartan has shown favorable pleiotropic effects in experimental and clinical studies conducted in endothelial cells, and its anti-inflammatory and antioxidant properties offer a beneficial effect in cardiac remodeling and renal and vascular function, thereby making it an ideal choice for BP control for patients with metabolic syndrome to further reduce the risk of ASCVD.[21]

The ADA guidelines recommend an ARB (or an ACE inhibitor) for patients with hypertension and diabetes with albuminuria (urinary albumin-to-creatinine ratio ≥30 mg/g). The ARBs improve kidney outcomes in patients with hypertension and CKD (the diabetic and nondiabetic population) (Figure 3).

Centrally acting antihypertensive agents work by reducing the sympathetic outflow via stimulating the alpha2-adrenergic receptors and/or imidazoline receptors on adrenergic neurons in the rostral ventrolateral medulla. Centrally-acting agents also stimulate the peripheral alpha2-receptors.[44] Alpha-methyldopa was the group prototype; however, its use has decreased significantly due to dose-dependent side effects. However, patients with resistant hypertension who require multidrug therapy, particularly those with CKD, are commonly responsive to these drugs so are patients with sympathetically mediated forms of hypertension. Clonidine, which belongs to the same group, is a preferred choice for perioperative hypertension and in patients with systolic heart failure with hypertension. The antihypertensive effect of clonidine-like centrally acting antihypertensive agents was attributed to both alpha2-adrenergic receptors and noradrenergic I (1)-imidazoline receptors. Activation of only alpha2-adrenergic receptors located in the locus coeruleus is responsible for sedation. Selective I (1) -imidazoline receptor ligands were found to reduce the incidence of typical side effects, which were seen with clonidine and alpha-methyldopa. Moxonidine is one such agent that has been effective in treating hypertension associated with diabetes, given its neutral or beneficial effects on the carbohydrate and lipid metabolism. It also has a beneficial effect on insulin resistance. Moreover, minimal dose-dependent reductions in fasting plasma glucose levels have been noted with moxonidine.[40]

CONCLUSION

The trio of diabetes, hypertension, and dyslipidemia is mutually aggravating, without monitoring one, the other two are difficult to control. Keeping this in mind, aggressive interventions to control each of these comorbidities are recommended for patients with diabetes to improve the outcome as well as to reduce the morbidity and mortality.

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