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Sweet taste disorder and vascular complications in patients with abnormal glucose tolerance

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ABSTRACT

Background: It remains unknown whether taste disorders can be a risk factor for micro- and macro-vascular diseases in patients with abnormal glucose tolerance.
Methods: A cross-sectional study in a nationally representative samples of 848 and 849 US adults (aged ≥40 years) with diabetes or prediabetes who had sweet and salt taste disorders, respectively, from the National Health and Nutrition Examination Survey 2011–2012.
Results: Among the study population, 5.7% had sweet taste disorder and 8.6% had salt taste disorder. These data correspond to approximately 1.5 million and 1.8 million individuals with abnormal glucose tolerance aged 40 years or older in the US population, respectively. In the adjusted model, sweet taste disorder was significantly associated with complication of ischemic heart disease (adjusted odds ratio [OR], 2.45; 95% confidence interval [CI], 1.03–5.81; P = 0.04). Moreover, sweet taste disorder in patients with diabetes was significantly associated with diabetic retinopathy (adjusted OR, 2.89; 95% CI, 1.09–7.69; P = 0.03) and diabetic nephropathy (adjusted OR, 3.17; 95% CI, 1.07–9.36; P = 0.03). Meanwhile, salt taste disorder was not significantly associated with diabetic retinopathy, diabetic nephropathy, ischemic heart disease, or stroke. Total sugar intake was significantly higher in patients with sweet taste disorder than in those without it, whereas total daily intake of carbohydrate did not differ significantly. No significant association was observed between salt taste disorder and daily intake of sodium after multivariate analysis.
Conclusions: Sweet taste disorder in patients with abnormal glucose tolerance was associated with increased sugar intake and vascular complications.

1. Introduction

Abnormal glucose tolerance is associated with micro- and macrovascular diseases [1–3]. To prevent vascular complications, appropriate management of atherogenic risk factors such as hyperglycemia and hypertension is needed [4]. Diet therapy is undoubtedly necessary for the management of patients with abnormal glucose tolerance [4]. Present recommendations have been clarified to emphasize that patients with abnormal glucose tolerance should limit or avoid intake of sugar-sweetened beverages and excess sodium to reduce risk of worsening the cardiometabolic risk profile [4,5]. However, a leading barrier to diet therapy in patients with abnormal glucose tolerance may be disorders of tastes such as sweet and salt [6–8]. These taste disorders can exist comorbidly in patients with diabetes [6,8] and can be seen earlier than other complications such as diabetic neuropathy [7]. The disorders of tastes such as sweet and salt in patients with abnormal glucose tolerance can negatively affect vascular complications; patients with sweet and salt taste disorders may be more likely to consume large quantities of sugar and sodium, leading to rapid increases in blood glucose and hypertension. In addition, sweet taste disorder may reflect impairment of the systemic sweet taste receptor, recently found and reported to be associated with decreased secretion of glucagon-like peptide 1 (GLP-1) [9] and increased glucose absorption [10]. However,

Abbreviations: GLP-1, glucagon-like peptide 1; NHANES, National Health and Nutrition Examination Survey; HbA1c, glycated A1c; GFR, glomerular filtration rate; NCHS, National Center for Health Statistics; MEC, mobile examination center; MDRD, Modification of Diet in Renal Disease; USDA, US Department of Agriculture; DHHS, Department of Health and Human Services.

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it remains unknown whether these taste disorders are risk factors for micro- and macro-vascular diseases in patients with abnormal glucose tolerance. The aim of this study was to investigate whether sweet and/or salt taste disorders are associated with micro- and macro-vascular diseases in patients with abnormal glucose tolerance.

2. Subjects and methods

2.1. Data sources and study population

This study is a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES). Written informed consent was obtained from all participants. The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the NHANES protocols. NHANES is conducted by the NCHS at the Centers for Disease Control and Prevention. It uses a stratified, multistage probability sampling design, which enables samples to represent the US civilian non-institutionalized population. Data are collected at homes and mobile examination centers (MECs). Blood specimens were collected during the MEC examination. Among adults participating in the NHANES survey during the 2011–2012 period, the unweighted response rate for household interviews was 72.6%; that for MEC examinations was 69.5%. We focused on patients with abnormal glucose tolerance, which was defined as self-reported diagnosis of prediabetes or diabetes. Among patients with prediabetes, patients whose glycated A1c (HbA1c) levels were ≥6.5% in this survey were regarded as having diabetes. In the analysis associated with sweet taste disorder, we excluded those with missing information on the sense of sweet taste (n = 105), which produced a final sample of 848 (Fig. 1). Similarly, in the analysis associated with salt taste disorder, 104 patients had missing information on the sense of salt taste, which resulted in a final sample of 849. Females who were pregnant at the time of examination were not included in the study population.

2.2. Sweet and salt taste disorders

We extracted information about sweet and salt taste disorders from the 2011–2012 NHANES taste questionnaire data. The data contained the results of interviews with adults aged ≥40 years about the sense of taste; these interviews were conducted in their homes by interviewers trained to question participants about the sense of taste. We defined sweet taste disorder as a condition in which the ability to taste sweetness was worse compared with that when the participant was 25 years old. Salt taste disorder was defined in a similar way to sweet taste disorder.

2.3. Vascular complications

As for the micro- and macro-vascular complications, diagnoses of diabetic retinopathy, diabetic nephropathy, ischemic heart disease, and stroke were identified. Diabetic retinopathy was confirmed by self-report. Diabetic nephropathy was defined as diabetes with macroalbuminuria (urine albumin ≥300 mg/g of creatinine) and an impaired glomerular filtration rate (estimated GFR <60 mL/min/1.73 m^2).[4] The estimated GFR was calculated using the following Modification of Diet in Renal Disease (MDRD) Study equation: estimated GFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ for female$) \times (1.212$ for African American). Serum creatinine, urine albumin, and creatinine were measured during the MEC examination in this survey. Ischemic heart disease was defined as myocardial infarction or angina pectoris. Ischemic heart disease and stroke were confirmed by the trained interviewers.

2.4. Food intake

All NHANES participants were eligible for two 24-hour dietary recall interviews. The dietary intake data are used to estimate the type and amount of foods and beverages consumed during the 24-h period prior to the interview and estimate daily total energy and intake of nutrients and other food components from those foods and beverages. The first dietary recall interview was conducted in person in the MEC examination, and the second interview was conducted by telephone 3 to 10 days later by trained interviewers; averages of the total nutrient intakes at the first and the second interviews were assumed as the daily intakes of each participant. For each participant, daily total nutrient intake from food and beverages were calculated on the average at the first and the second interview. The dietary interview component was conducted as a partnership between the US Department of Agriculture (USDA) and the US Department of Health and Human Services

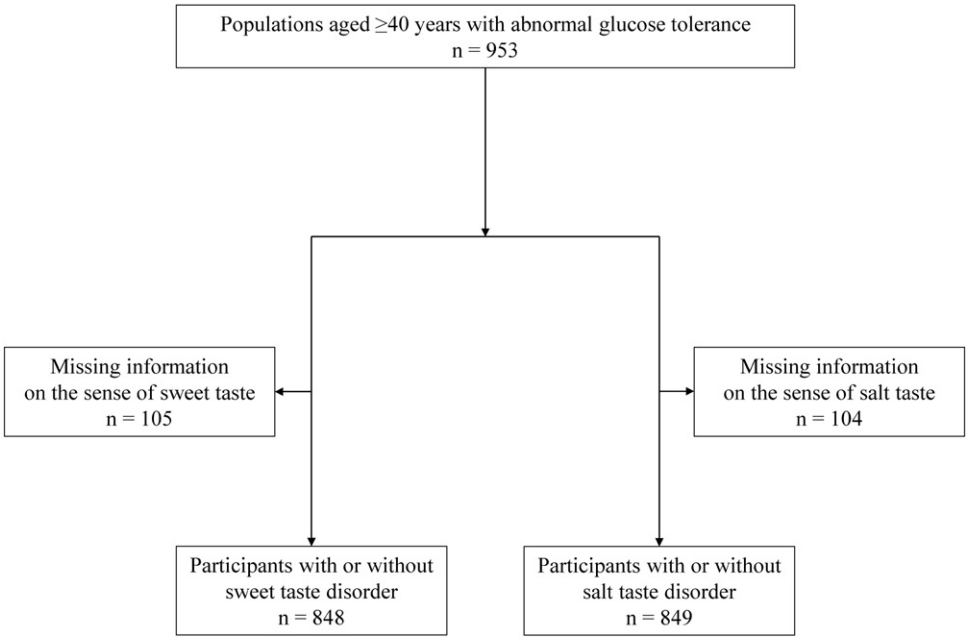

Fig. 1. Participant flow chart.

(DHHS). Interview data files were sent electronically from the field and were imported into Survey Net, a computer-assisted food coding and data management system developed by USDA. The USDA dietary data collection instrument, the Automated Multiple-Pass Method (AMPM), was designed to provide an efficient and accurate means of collecting intakes for large-scale national surveys.

2.5. Potential confounders

We extracted data on potential confounders including age, sex, race and ethnicity, obesity, smoking status, duration of diabetes, HbA1c, and diagnosis of hypertension and hyperlipidemia. For the purpose of following analyses, age was divided into two groups according to a cutoff level of 60 years, which approximated the overall mean value and was associated with altered taste sensation [11]. Race and ethnicity were classified into non-Hispanic white, non-Hispanic black, Mexican American, and others including other Hispanics and multiracial participants. Obesity was defined as body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 30 kg/m^2 or higher, using the measurements at the MEC examination. Duration of diabetes was divided into two groups, according to a cutoff level of 10 years. HbA1c was derived from the laboratory examination at the MEC. We defined hypertension and hyperlipidemia as self-reported diagnosis of hypertension and hyperlipidemia.

2.6. Statistical analysis

All statistical analyses were conducted using Stata (version 12.1; StataCorp LP), accounting for the complex survey design. We used an appropriate weight for each analysis selected based on the variables in the analysis. These weights accounted for unequal probabilities of selection and nonresponses to make unbiased national estimates. First, demographic statistics presented as the number (%) and mean with standard deviation were compared between those with and those without taste disorders. We repeated analyses for sweet and salt taste disorders separately. In addition, rate of daily sodium intake of less than 2.3 g/day, which is recommended by current guidelines [4,5], is assessed in patients with salt taste disorder. Continuous variables were compared using *t*-tests and categorical variables were compared using chi-square tests.

To assess the association between taste disorders and vascular complications, multivariate logistic-regression analyses were performed for patients with abnormal glucose tolerance. In addition, we performed the same analyses restricted to those with diabetes. We included age, sex, race and ethnicity, obesity, current smoking, hypertension, hyperlipidemia, and HbA1c level for adjustment. Duration of diabetes was added for the multivariate analyses in patients with diabetes. We also performed multiple regression analyses to evaluate the association between taste disorders and total daily energy and intakes of carbohydrate, sugar, and sodium. P values <0.05 were considered statistically significant for all tests.

3. Results

Of the populations aged ≥40 years with abnormal glucose tolerance in this study in the NHANES, 5.7% had sweet taste disorder and 8.6% had salt taste disorder. These data correspond to approximately 1.5 million and 1.8 million individuals, respectively with abnormal glucose tolerance aged ≥40 years in the US population [12]. The characteristics of the study population with or without sweet taste disorder are presented in Table 1. Among the population, age and proportion of females were significantly higher in patients with sweet taste disorder than in those without it. BMI was significantly lower in patients with sweet taste disorder than in those without it. Prevalence of diabetes and HbA1c levels was not significantly different between those with and those without sweet taste disorder. Ischemic heart disease was more complicated in patients with sweet taste disorder than in those without it (34.3% vs. 13.4%, P = 0.01). The complication rates of microvascular diseases were significantly higher in patients with sweet taste disorder than in those without it (42.4% vs. 13.7% for diabetic retinopathy [P < 0.001] and 11.6% vs. 2.4% for diabetic nephropathy [P = 0.01]), but that of stroke did not differ significantly between the two groups. Total daily intake of carbohydrate was lower in patients with sweet taste disorder, whereas that of sugar was higher in patients with sweet taste disorder. Although these values were not significantly different, the ratio of sugar to carbohydrate was significantly higher in patients with sweet taste disorder than in those without it (0.47 [0.14] vs. 0.38 [0.13], P = 0.004).

Table 1
Characteristics of US adults aged 40 years or older with abnormal glucose tolerance stratified by the presence/absence of sweet taste disorder.[a]

Characteristics	Sweet taste disorder (+)	Sweet taste disorder (−)	P value
Unweighted sample, no. (%)	48 (5.7%)	800 (94.3%)	
Age range (y)	64.6 (10.5)	60.9 (12.6)	0.004
Female sex	69.6%	52.3%	0.04
Race/ethnicity			
Non-Hispanic white	66.6%	62.4%	0.66
Non-Hispanic black	19.1%	15.3%	0.50
Mexican American	5.8%	6.9%	0.80
Others[b]	8.5%	15.4%	0.27
Body mass index (kg/m^2)	30.1 (6.1)	32.8 (8.2)	0.01
Obesity	50.0%	61.0%	0.19
Current smoking	6.1%	14.2%	0.17
Hypertension	74.7%	68.7%	0.55
Hypercholesteremia	78.2%	66.1%	0.15
Diabetes	71.4%	75.0%	0.68
Duration of diabetes (y) ≥ 10	68.1%	45.9%	0.09
HbA1c (%)	6.8 (2.1)	6.9 (1.7)	0.75
Vascular complications			
Ischemic heart disease	34.4%	13.4%	0.01
Stroke	9.2%	6.5%	0.55
Diabetic retinopathy	42.4%	13.7%	<0.001
Diabetic nephropathy	11.6%	2.4%	0.01
Total daily intakes			
Carbohydrate (g)	207.2 (85.5)	228.3 (99.4)	0.25
Sugar (g)	98.1 (47.4)	89.4 (53.3)	0.30
Sugar/carbohydrate ratio	0.47 (0.14)	0.38 (0.13)	0.004

Abbreviation: HbA1c, glycated A1c.
[a] Data are represented as number, percent, or mean (SD).
[b] The category includes other Hispanics and other races including multi-racial participants.

The characteristics of the study population with or without salt taste disorder are shown in Table 2. Proportion of females and prevalence of hypertension were significantly higher in patients with salt taste disorder than in those without it. The complication rate of diabetic retinopathy was significantly higher in patients with salt taste disorder (30.8% vs. 14.0%, P = 0.02). Although diabetic nephropathy, ischemic heart disease, and stroke were more complicated in patients with salt taste disorder than in those without it, the differences were insignificant. Total daily intake of sodium was significantly lower in patients with salt taste disorder than in those without it (2.8 [1.3] g vs. 3.4 [1.5] g, P = 0.001).

Associations between taste disorders and vascular complications are presented in Table 3. When multivariate logistic-regression analyses were performed in patients with abnormal glucose tolerance, the complication of ischemic heart disease was significantly associated with sweet taste disorder (adjusted odds ratio [OR], 2.45; 95% confidence interval [CI], 1.03–5.81; P = 0.04). Similarly, multivariate logistic-regression analyses in the diabetic patients revealed that sweet taste disorder was significantly associated with diabetic retinopathy (adjusted OR, 2.89; 95% CI, 1.09–7.69; P = 0.03) and diabetic nephropathy (adjusted OR, 3.17; 95% CI, 1.07–9.36; P = 0.03). Although ischemic heart disease was more complicated in diabetic patients with sweet taste disorder, no significant association was observed. Meanwhile, salt taste disorder was not significantly associated with diabetic

Table 2
Characteristics of US adults aged 40 years or older with abnormal glucose tolerance stratified by the presence/absence of salt taste disorder.[a]

Characteristics	Salt taste disorder (+)	Salt taste disorder (−)	P value
Unweighted sample, no. (%)	73 (8.6%)	776 (91.4%)	
Age range (y)	64.7 (14.4)	60.9 (12.3)	0.07
Female sex	72.6%	52.0%	0.02
Race/ethnicity			
Non-Hispanic white	50.8%	63.6%	0.17
Non-Hispanic black	19.1%	15.2%	0.42
Mexican American	10.5%	6.5%	0.21
Others[b]	19.6%	14.7%	0.43
Body mass index (kg/m^2)	32.7 (9.2)	32.6 (7.8)	0.92
Obesity	60.7%	60.5%	0.97
Current smoking	15.5%	13.6%	0.61
Hypertension	87.3%	67.7%	0.02
Hypercholesteremia	69.4%	66.6%	0.71
Diabetes	81.5%	74.4	0.30
Duration of diabetes (y) ≥ 10	67.2%	45.6%	0.04
HbA1c (%)	7.6 (2.5)	6.9 (1.7)	0.09
Vascular complications			
Ischemic heart disease	22.9%	13.9%	0.05
Stroke	7.9%	6.6%	0.63
Diabetic retinopathy	30.8%	14.0%	0.02
Diabetic nephropathy	6.7%	2.6%	0.17
Total daily intakes			
Sodium (g)	2.8 (1.3)	3.4 (1.5)	0.001
<2.3 (g)[c]	36.0%	20.6%	0.04

[a] Data are represented as number, percent, or mean (SD). HbA1c, glycated A1c.
[b] The category includes other Hispanics and other races including multiracial participants.
[c] The sodium intake of less than 2.3 g/day is recommended by American Diabetes Association. To convert sodium to salt, multiply by 2.54.

retinopathy, diabetic nephropathy, ischemic heart disease, or stroke for those having abnormal glucose tolerance or for those having diabetes.

We evaluated the association between taste disorders and total daily intakes of carbohydrate, sugar, and sodium, using multivariate regression analyses. In both the abnormal glucose tolerance and diabetes groups, total sugar intake was significantly higher in patients with sweet taste disorder than in those without it (P = 0.03 and P = 0.01, respectively). Total daily intakes of carbohydrate and sodium did not differ significantly between patients with and without sweet taste disorder. No significant association was observed between salt taste disorder and intakes of carbohydrate, sugar, and sodium.

Table 3
Adjusted associations between taste disorders and vascular complications.[†]

Event	Sweet taste disorder		Salt taste disorder	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Participants with abnormal glucose tolerance[††]				
Ischemic heart disease	**2.96 (1.07–8.19)**	**0.03**	1.54 (0.69–3.42)	0.26
Stroke	0.80 (0.20–3.18)	0.74	0.70 (0.18–2.61)	0.57
Participants with diabetes				
Diabetic retinopathy	**2.89 (1.09–7.69)**	**0.03**	2.50 (0.89–7.04)	0.07
Diabetic nephropathy	**3.17 (1.07–9.36)**	**0.03**	1.51 (0.56–4.05)	0.38
Ischemic heart disease	2.23 (0.66–7.56)	0.18	1.33 (0.65–2.72)	0.41
Stroke	0.78 (0.21–2.83)	0.69	0.69 (0.17–2.82)	0.59

Abbreviations: OR, odds ratio; CI, confidence interval.
Bold type indicates a significant association (P < 0.05).
[†] Odds ratio was adjusted for age, sex, race and ethnicity, obesity, current smoking, hypertension, hyperlipidemia, and HbA1c level in patients with abnormal glucose tolerance. Duration of diabetes was added for the adjustment in patients with diabetes.
[††] Abnormal glucose tolerance included prediabetes and diabetes.

4. Discussion

To our knowledge, this is the first large-scale study to report that sweet taste disorder in patients with abnormal glucose tolerance and diabetes is associated with vascular complications. In addition, this study revealed that daily sugar intake is significantly higher in patients with sweet taste disorder than in those without it, even though the total carbohydrate intake did not show significant differences. On the other hand, an association between salt taste disorder and vascular complications was not observed, and daily intake, including sodium, was not significantly different.

Taste disorders can be a complication in patients with abnormal glucose tolerance [6–8]. In particular, sweet taste disorder may be a notable complication in patients with abnormal glucose tolerance. Sweet taste disorder in patients with abnormal glucose tolerance was associated with increased sugar intake. Large quantities of sugar can contribute to risk of vascular damage, partly by their ability to contribute to obesity, but an independent effect may also stem from the high amounts of rapidly absorbable carbohydrates [13–15]. Excess consumption of sugar has been shown to result in rapid and dramatic increases in blood glucose and insulin concentrations [13]. A large and growing body of evidence shows that postprandial hyperglycemia is associated with microvascular diseases [16,17], cardiovascular disease [18,19], and mortality [20]. Moreover, recent studies suggest that postprandial hyperglycemia is also linked to cognitive dysfunction in elderly people [21], and certain cancers [22]. According to the results of many fundamental studies, the main mechanism through which acute hyperglycemia exerts harmful effects on diabetic complications may be identified in the production of free radicals [18]. Because significant evidence has demonstrated the harmful effects of postprandial hyperglycemia, special attention should be paid to patients with sweet taste disorder. Meanwhile, salt taste disorder was not associated with vascular complications or daily intake of sodium in the multivariate analyses. Patients with abnormal glucose tolerance may adequately regulate daily sodium intake independently of salt taste disorder.

The sensitivity of taste in patients with abnormal glucose tolerance can be influenced not only by aging and smoking [11,23] but also the complication of diabetic neuropathy [24]. However, a previous study reported that patients with newly-diagnosed diabetes, who had no clinical evidence of diabetes-related complications, also showed impaired taste [7]. In addition, a direct effect of blood glucose concentration on taste may be unlikely [25]. Therefore, the opposite causal path may be more plausible; inherent or acquired impairment of the taste receptor may lead to taste disorder. The receptors of basic five tastes—sweet, salt, bitter, sour, and umami, are mediated by separate populations of selectively tuned taste receptor cells [26–28]. Importantly, recent studies revealed that cells with taste receptors were not restricted to the taste buds of the tongue and these receptors elaborately control the intake and absorption to maintain homeostasis [29,30]. The sweet taste receptor, T1R2/T1R3, is also found in the intestine. Some studies suggested that sweet taste receptors on L-type enteroendocrine cells in the intestine are linked to glucagon-like peptide 1 (GLP-1) secretion, which in turn stimulates insulin production [9]. In addition, a recent study reported that the dysregulation of intestinal sweet taste receptors may enhance glucose absorption and exacerbate postprandial hyperglycemia in patients with type 2 diabetes [10]. Therefore, if sweet taste disorders in patients with abnormal glucose tolerance reflect the systemic impairment of sweet taste receptors, postprandial hyperglycemia may not stem solely from sugar intake. In particular, those with sweet taste disorder in this study might actually have impaired sweet taste receptors in both the tongue and intestine. As a result, increased sugar intake, reduced secretion of GLP-1, and enhanced absorption of glucose might lead to greater fluctuations in

blood glucose and increased vascular complications. Further studies are needed to reveal the association between sweet taste disorder and vascular complications.

This study has several limitations. First, the present study investigated self-reported disorders of taste that were evaluated by comparison with the participants' ability to taste at 25 years old. More objective examinations for the ability to taste may be needed to reveal the association between taste disorders and vascular complications. However, because established methods to assess taste disorders are lacking in daily clinical settings, the evaluation method of taste sensation in this study may be a realistic option for risk assessment of vascular complications. Second, the cross-sectional nature of the NHANES precludes us from drawing firm conclusions, regarding the association between taste disorders and vascular complications. Therefore, some prospective, large-scale, multicenter studies will be required to confirm our results. Finally, the numbers of patients with taste disorders were small, which could influence multivariate analyses. However, this study was performed based on the national survey of US adults and several studies have supported our results. Therefore, we believe that our study provides extremely important and novel information about the association between sweet taste disorder and vascular complications in patients with abnormal glucose tolerance.

In conclusion, sweet taste disorder in patients with abnormal glucose tolerance was associated with increased sugar intake and vascular complications, whereas salt taste disorder was not associated with daily sodium intake and vascular complications. Further investigation about sweet taste disorder may lead to better medical care for patients with abnormal glucose tolerance.

Conflict of interest disclosures

The authors report no relationships that could be construed as a conflict of interest. No financial disclosures were reported.

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Dr. Tsujimoto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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