

# Fasting plasma glucose levels and coronary artery calcification in subjects with impaired fasting glucose

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**BACKGROUND:** Prediabetes is associated with an increased risk of cardiovascular disease (CVD). While the association of impaired glucose tolerance with CVD has been shown in many studies, the relationship between impaired fasting glucose (IFG) and CVD remains unclear.

**OBJECTIVES:** The purpose of this study was to compare the coronary artery calcium (CAC) scores of participants with normal fasting glucose versus those with IFG, according to fasting plasma glucose (FPG) levels, and to assess whether differences in CAC scores were independent of important confounders.

**DESIGN:** Retrospective study.

**SETTING:** Health Promotion Center of the University Hospital (Gyeonggi-do, South Korea), during the period 2010–2014.

**PATIENTS AND METHODS:** Participants were enrolled from the general population who visited for a medical check-up. CAC was assessed in asymptomatic individuals by multidetector computed tomography. Anthropometric parameters and metabolic profiles were also recorded. Subjects were divided into four fasting glucose groups. Participants with a history of CVD or diabetes mellitus were excluded.

**MAIN OUTCOME MEASURES:** Correlation between FPG and CAC scores, CAC score categories, and association between CAC score and FPG categories.

**RESULTS:** Of 1112 participants, 346 (34.2%) had a CAC score >0. FPG values in the IFG patients were positively but weakly correlated with CAC scores ( $r=0.099$ ,  $P=.001$ ). The incidence of CAC differed according to FPG level ( $P<.001$ ) and in Kruskal-Wallis test the mean CAC score differed by FPG group ( $P<.001$ ). After adjustment for other factors in a multiple logistic regression analysis, those subjects with  $FPG \geq 110$  mg/dL had a significantly higher risk of CAC than did subjects with normal fasting glucose ( $110 \leq FPG$  [mg/dL] <120,  $OR=2.507$ ,  $P=.002$ ;  $120 \leq FPG$  [mg/dL] <126,  $OR=3.568$ ,  $P=.001$  vs. <100 mg/dL).

**CONCLUSION:** IFG (especially  $FPG \geq 110$  mg/dL) could be an independent risk factor for CAC. These associations were not altered after adjustment for other possible confounders.

**LIMITATIONS:** Possible misclassification because data taken from a single blood test. No HbA1c tests or repeated FPG tests. No adjustment for other potentially important confounders.

The three leading causes of death in Korea are cancer, cerebrovascular disease, and cardiovascular (CVD) disease. As the mean age of the population in Korea has increased, the prevalence of diabetes mellitus (DM) has increased to 12%. The prevalence of coronary artery disease (CAD) has grown as well. In patients with DM, CVD is a major cause of death and accounts for a large portion of medical costs.<sup>1</sup> As with other diseases, prevention, followed by early detection and early

treatment, are most important in addressing CAD and CVD. Korea's national health insurance service provides for a biennial health examination, including fasting plasma glucose (FPG) and lipid profile measurements, for adults older than 30 years to promote early detection of CAD and to control risks. Through this health check-up, diabetic patients can be diagnosed early and cared for properly. However, most patients with IFG are not included in the consideration of DM or CAD risk.

Patients with IFG are at high risk for DM.<sup>2</sup> Since the incidence of macrovascular complications is only weakly associated with the duration of diabetes, one may speculate that impaired glucose homeostasis and increasing atherogenicity occur prior to a clinical diagnosis of DM.<sup>3</sup> To better manage patients at high risk for future cardiac events, the identification of subclinical atherosclerosis in patients with prediabetic status has important implications.

Coronary angiography is the gold standard for diagnosis of coronary artery disease, but its invasiveness prevents its regular use in asymptomatic patients.<sup>4</sup> The coronary artery calcium (CAC) score is a good surrogate marker for the presence and extent of coronary atherosclerosis.<sup>5</sup> Major studies have indicated that CAC scores could be used in the future to predict risk rates for CAD. In 2010, the American College of Cardiology/American Heart Association indicated that CAC measurement is a reasonable method to assess cardiovascular risks for asymptomatic adults in the Framingham intermediate risk group (10-20% 10-year risk).<sup>6</sup>

In 1997, the American Diabetes Association (ADA) introduced the concept of IFG as an intermediate state of abnormal glucose regulation.<sup>7-10</sup> The blood glucose range for IFG was lowered in 2003, from 110-125 mg/dL to 100-125 mg/dL, as an effort to better identify individuals at future diabetes risk. Lowering the cutoff for IFG was intended to motivate individuals with IFG to adopt early lifestyle interventions to reduce potential risks of developing diabetes in the future.<sup>11</sup> However, some experts have not supported this decision.<sup>12</sup> As a result, the predictive value of IFG coronary heart disease (CHD) risk has changed. In the Hoorn Study, a lower cutoff for IFG (ADA 2003 criteria) resulted in an increase in the prevalence of IFG (10.1% to 33.2%) and a reduction in the incidence rate of diabetes (42% to 21%). Furthermore, the hazard ratios of all-cause and cardiovascular mortality were lower for 2003 criteria than for 1997 (hazard ratio for CVD mortality, 1.87 [95% CI 1.07-3.25] and 1.37 [95% CI 0.87-2.16]).<sup>13</sup> In another study with a four-year follow up, the CHD risk was greater in women with IFG based upon the 1997 compared with the 2003 criteria (odds ratio 2.2 [95% CI 1.1-4.4] and 1.7 [95% CI 1.0-3.0], respectively).<sup>14</sup>

Many reports have suggested a correlation between IFG and CVD, but the quality of previous data is variable. Methodological problems, such as lack of exclusion of subjects with DM and use of different fasting plasma glucose (FPG) ranges for IFG, were present in some studies.<sup>13,15,16</sup> There remains uncertainty regarding the association of IFG with CHD risk<sup>17</sup> and, specifically, whether IFG is an independent risk factor for CAC.

Therefore, the aims of this study were to compare the CAC scores of participants with normal fasting glucose versus those with IFG, according to FPG levels, and to assess whether differences in CAC score were independent of important confounders.

## PATIENTS AND METHODS

We enrolled subjects from among those members of the general population who visited the Health Promotion Center of the University Hospital (Gyeonggi-do, Republic of Korea), for a medical check-up and coronary artery multidetector computed tomography (MDCT). Subjects were excluded who were diagnosed with diabetes mellitus or undergoing diabetes treatment with oral agents or insulin, or who had symptoms of CAD. This study was conducted in accordance with the ethical and safety guidelines approved by the Institutional Review Board of the Catholic University of Korea, St. Vincent's Hospital (IRB approval number: VCRASI0112). The study qualified for exemption from the written informed consent requirement of the participants, because we reviewed health screening data and medical records retrospectively. All of the data records were de-identified and analyzed anonymously. The IRB approved this consent procedure.

Before undergoing physical examinations, subjects self-reported their medical history including hypertension, diabetes mellitus, angina pectoris, and myocardial infarction. They also provided information about their medication history, as well as their smoking status, alcohol intake, and exercise habits. Body mass index (BMI) and body composition were measured by InBody 3.0 (Biospace, Korea), which uses bioelectrical impedance analysis. Waist circumference (WC) was measured at the narrowest point between the lower limits of the ribcage and iliac crest. Blood pressure was measured and recorded using an automatic manometer between 08:00 and 10:00 a.m., after each subject was allowed to relax for at least 10 minutes. Hypertension was defined by two serial systolic/diastolic blood pressure measures  $\geq 140/90$  mm Hg or by treatment with antihypertensive medication.

Blood samples were collected on the day of examination after at least 8 hours of fasting, and an automatic clinical chemistry analyzer (Sysmex XE-2100; Japan, and Hitachi 7600; Japan) was used to analyze fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels for each sample. Normal fasting glucose (NFG) was defined as a level of  $<100$  mg/dL and IFG as 100-125 mg/dL; diabetes was defined as a fasting glucose level  $\geq 126$  mg/dL or by

current diabetes treatment with oral glucose-lowering agents or insulin.<sup>18</sup> To examine in detail the nature of any association across distributions of FPG and CAC score, study subjects were divided into four groups according to glucose level (<100, 100-109, 110-119, and 120-125 mg/dL).

### Coronary artery calcification test

To calculate CAC, we used 64-slice multidetector CT scanners (Sensation 64, Siemens, Erlangen, Germany). All subjects fasted for at least 6 hours prior to examination, and those with heart rates >65 beats/min received a  $\beta$ -blocker to lower their heart rate for testing. Subjects received one 60-70-mL dose of nonionic contrast (Ultavist 370, Schering, Germany) by injection, followed

by 40 mL saline. After obtaining images via electrocardiogram synchronization, CAC was quantified using a reconstruction program (Wizard, Siemens, Erlangen, Germany). CAC scores were measured based on the standards of the Agatston Score.<sup>5</sup> This method divides the coronary arteries into right, left main, left anterior, and left circumflex, then quantifies each artery, and adds all four scores to calculate the CAC score. For this study, CAC was considered to be present if the CAC score was greater than 0. When categorizing the CAC score according to severity, we used the Rumberger criteria<sup>19</sup> which defines CAC scores of 0 HU as none, of 1-10 HU as minimal, 11-99 HU as mild, 100-399 HU as moderate, and  $\geq$ 400 HU as severe. MDCT and blood sampling were performed on the same day.

### Statistical analysis

All data are presented as means and standard deviation or numbers and percent. The correlation of CAC scores with fasting glucose and other factors was tested using the Pearson correlation. Because CAC scores were not normally distributed, the Kruskal-Wallis rank sum test was used to assess differences in CAC scores by quartiles of FPG. A post-hoc test was used to assess which groups were different. The chi-square test was used to analyze differences in CAC dispersion by FPG level under the 2003 and 1997 ADA criteria. Multiple logistic regression analysis was performed to identify variables related to a CAC score >0 and to analyze the association between IFG and CAC.

Statistical significance was defined as  $P < .05$ . All analyses were performed using the SPSS 18.0 software package (SPSS, Inc., Chicago, IL, USA).

## RESULTS

1112 adults were screened between 2 January 2010 and 30 November 2014, and 88 were excluded. Twelve additional subjects were diagnosed with CAD or had symptoms suspicious of CAD before enrollment. Of 1112 participants, 346 (31.1%) had a CAC score >0 (**Table 1**). A higher prevalence of CAC was observed among men than women (266 [34.3%] vs. 80 [23.7%]). The incidence of CAC was higher in smokers than in non-smokers (231 [34.7%] vs. 115 [25.7%]). Participants with a CAC score >0 had higher mean BMIs and WCs than those without CAC. Accordingly, more participants with a CAC score >0 were classified as obese (BMI  $\geq$ 25 kg/m<sup>2</sup>). In addition, participants with a CAC score >0 were more likely to be older and hypertensive (systolic). FPG, total cholesterol, triglycerides, LDL cholesterol, and r-glutamyl transpeptidase (rGTP) were significantly higher in subjects with CAC. CAC scores showed a

**Table 1.** Characteristics of the study population according to CAC score.

	CAC score=0 (n=766)	CAC score >0 (n=346)	P
Age (years)	51.9 (9.1)	58.7 (9.0)	<.001
Sex			<.001
Men	509 (65.7%)	266 (34.3%)	
Women	257 (76.3%)	80 (23.7%)	
Smoking <sup>a</sup>			.002
Non smoker	332 (74.3%)	115 (25.7%)	
Smoker	434 (65.3%)	231 (34.7%)	
WC (cm)	85.7 (8.5)	88.5 (8.8)	<.001
BMI (kg/m <sup>2</sup> )	24.7 (3.2)	25.4 (2.9)	<.001
SBP (mmHg)	126.4 (14.1)	131.0 (13.7)	<.001
DBP (mmHg)	77.4 (10.1)	78.5 (9.5)	.088
FPG (mg/dL)	97.5 (20.4)	104.8 (25.5)	<.001
Total cholesterol (mg/dL)	202.2 (35.9)	209.0 (39.6)	.007
Triglyceride (mg/dL)	137.7 (89.7)	151.2 (83.9)	.017
LDL-cholesterol (mg/dL)	122.6 (32.4)	127.2 (35.2)	.038
HDL-cholesterol (mg/dL)	46.1 (11.3)	45.6 (11.3)	.498
rGTP (U/L)	37.7 (41.1)	47.0 (53.4)	.004
AST (IU/L)	22.9 (9.6)	23.9 (8.6)	.093
ALT (IU/L)	27.8 (18.6)	28.0 (15.4)	.896

Data are expressed as mean (standard deviation) or N (%); P values were obtained by independent t test or  $\chi^2$ -test; <sup>a</sup>Included ex-smokers. WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; rGTP,  $\gamma$ -glutamyl transpeptidase; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase.

weak but significant positive correlation with FPG, age, and BMI (**Table 2**).

The number of IFG participants was 299 (29.2%) by the 2003 ADA definition, which is similar to the IFG prevalence for people older than 50 years of age in Korea.<sup>20</sup> At the baseline visit, 716 (69.9%) participants had none, 100 (9.8%) had minimal, 143 (14.0%) had mild, 46 (4.5%) had moderate, and 19 (1.9%) had severe CAC according to Rumberger category. When the prevalence of IFG by both criteria (1997 vs 2003 ADA) and CAC categories were compared, IFG increased with CAC severity (**Table 3**). Using the chi-

**Table 2.** The correlations coefficient (r) between CAC score and other co-factor.

	r	P
FPG (mg/dL)	.099	.001
Age	.169	<.001
BMI (kg/m <sup>2</sup> )	.065	.03
SBP (mmHg)	.058	.054
DBP (mmHg)	-.009	.769
Triglyceride (mg/dL)	.011	.703
LDL-cholesterol (mg/dL)	-.042	.16
HDL-cholesterol (mg/dL)	-.008	.793
AST (IU/L)	.023	.436
ALT (IU/L)	-.007	.808
rGTP (U/L)	.021	.494

P values were obtained by Pearson correlation analysis. FPG, fasting blood glucose; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; rGTP,  $\gamma$ -glutamyl transpeptidase

square test, we observed differences in the incidence of CAC according to FPG levels in the non-diabetic range ( $P<.001$ ). The Kruskal-Wallis rank sum test indicated that the median CAC scores differed between the FPG groups ( $P<.001$ ) (**Table 4**). The Dunn test indicated that differences between the <100, the 100-109 and 110-119 groups were statistically significant.

Using multivariate logistic regression models, we examined independent risk factors for the presence of CAC (**Table 5**). After adjustment for age, gender, BMI, WC, systolic blood pressure, diastolic blood pressure, smoking, and levels of triglycerides, HDL- and LDL-cholesterol, aspartate transaminase, alanine transaminase, and rGTP, the subjects with a FPG $\geq$ 110 mg/dL had a significantly higher risk of having a CAC score >0 than those with normal FPG levels (110 $\leq$ FPG [mg/dL] <120 group: OR=2.507,  $P=.002$ ; 120 $\leq$ FPG [mg/dL] <126 group: OR=3.568,  $P=.001$  vs <100 mg/dL) Older age and male gender (OR=1.111,  $P<.001$  for age; OR=0.36,  $P<.001$  for gender) were found to increase the risk of CAC. Higher BMI, higher systolic blood pressure, higher triglyceride, LDL-cholesterol, and rGTP levels were also significant predictive factors for CAC. The model explained 24% to 33% of the variability and was a good fit for the data.

## DISCUSSION

The major findings of our study included a positive correlation between FPG in the prediabetic range and CAC and the suggestion that IFG (especially FPG $\geq$ 110 mg/dL) may be an independent risk factor for the presence of CAC. These associations did not change appreciably after adjustment for other possible confounders. Our study supports the idea that CAC already exists in the pre-diabetic state, and that IFG $\geq$ 110 mg/dL has an independent influence on the atherosclerotic process.

**Table 3.** The correlations between IFG and CAC score categories.

	CAC score category					P
	Non	Minimal	Mild	Moderate	Severe	
<b>2003 ADA criteria</b>						
FPG (mg/dL) <100	542 (74.8)	66 (9.1)	84 (11.6)	23 (3.2)	10 (1.4)	<.001
FPG (mg/dL) $\geq$ 100	174 (58.2)	34 (11.4)	59 (19.7)	23 (7.7)	9 (3.0)	
<b>1997 ADA criteria</b>						
FPG (mg/dL) <110	673 (72.8)	88 (9.5)	113 (12.2)	37 (4.0)	14 (1.5)	<.001
FPG (mg/dL) $\geq$ 110	43 (43.4)	12 (12.1)	30 (30.3)	9 (9.1)	5 (5.1)	

Data are expressed as n (%). P values were obtained by  $\chi^2$ -test; CAC, coronary artery calcium; FPG, fasting plasma glucose (mg/dL).

The ADA 2015 guidelines recommend that patients with IFG should undergo counseling on lifestyle changes and should increase moderate-intensity physical activities to at least 150 minutes/week.<sup>21</sup> The guidelines also recommend screening for CVD and treatment to correct risk factors (evidence B). Thus, IFG patients need to be evaluated for CAD risk and to

take preventive efforts at an early stage.

Many studies have investigated the influence of abnormal glucose homeostasis on the risk of subclinical atherosclerosis or CVD.<sup>3</sup> In China, a weak association was observed between IFG and CVD,<sup>22</sup> and the AusDiab study observed a J-shaped relationship between FPG and CVD mortality.<sup>23</sup> In a meta-analysis of 18 publications with information on IFG (110 to 125 mg/dL), the estimated relative risk (RR) for CVD was 1.20 (95% confidence interval [CI]: 1.12-1.28). In eight publications with analysis of IFG (100 to 125 mg/dL), the estimated RR for CVD was not statistically significant (RR 1.16, 95% CI 0.94-1.42).<sup>15</sup> However, the WOSCOPS study analyzed the relationship between FPG and CVD events, as well as all-cause mortality, in 6447 men with hypercholesterolemia from Western countries. They clearly demonstrated that FPG in the prediabetic range was not associated with an increased risk of CVD events, CHD death, or all-cause mortality.<sup>17</sup>

In the Heinz Nixdorf Recall Study, which enrolled 2184 participants,<sup>3</sup> IFG was associated with the prevalence of CAC in men but not in women, after adjustment for potential confounders including BMI. Lee et al reported that when FPG was elevated more than 100 mg/dL, the odds ratio for CAC increased in adult Korean males (OR: 2.00; 95% CI: 1.36–2.94).<sup>24</sup> However, in a subsample of the Framingham Heart Study, IFG was not associated with CAC, after adjustment for other risk factors with obesity.<sup>25</sup> Thus there is a great diversity of opinion on the relationship between IFG and CAC or CAD. Even so, it is obvious that FPG is a good screening tool because of the convenience and economic efficiency. A means for improving the accuracy to predict CAD in patients with IFG is needed.

In the Hoorn Study, a lower cutoff for IFG (ADA 2003 criteria) resulted in a category of IFG no longer encompassing patients with a higher risk of CVD.<sup>13</sup> A meta-analysis from China found that prediabetes defined as IFG $\geq$ 110 mg/dL was associated with an increased risk of all-cause and cardiovascular mortality. However, IFG $\geq$ 100 mg/dL was not associated with all-cause or cardiovascular mortality in the overall analysis.<sup>16</sup> The results of these studies correspond with those of the present study showing that CAC correlates with an IFG $\geq$ 110 mg/dL. These results emphasize the need for an FPG level-specific analysis, at least when it comes to determining CAC as an outcome.

Lipid parameters also have an important role in CAD. In the Multi-Ethnic Study of Atherosclerosis (MESA), triglycerides, LDL cholesterol and HDL cholesterol were associated with a risk of incident CAC.<sup>26</sup> LDL-cholesterol

**Table 4.** Associations of fasting plasma glucose by quartiles with CAC score level.

	Median
FPG (mg/dl) <100 <sup>a</sup>	24.0
100 $\leq$ FPG (mg/dL)<110 <sup>a</sup>	35.5
110 $\leq$ FPG (mg/dL)<120 <sup>a</sup>	22.5
120 $\leq$ FPG (mg/dL)<126	34.0

CAC, coronary artery calcium; FPG, fasting plasma glucose (mg/dL); Kruskal-Wallis rank sum test chi-squared=175.71, df=104, P<.001; Levene test: 14.537, df1=3, df2=1020, (P<.001). <sup>a</sup>FPG groups different (Dunn test with Bonferroni correction, P<.001)

**Table 5.** Results from the multiple logistic regression models for variables associated with the presence of coronary calcification (CAC score=0 or >0).

	Odds ratio	CI (95%)		P
		Lower	Upper	
FPG(<100 mg/dL)				
100 $\leq$ FPG<110	0.925	0.630	1.356	.689
110 $\leq$ FPG<120	2.507	1.390	4.521	.002
120 $\leq$ FPG<126	3.568	1.648	7.727	.001
Female	0.36	0.214	0.605	<.001
Age (years)	1.111	1.088	1.134	<.001
Smoking	1.023	0.643	1.63	.922
BMI (kg/m <sup>2</sup> )	1.069	1.012	1.129	.017
SBP (mmHg)	1.021	1.003	1.04	.023
DBP (mmHg)	0.978	0.953	1.003	.084
TG (mg/dL)	1.002	1.000	1.004	.023
LDL (mg/dL)	1.01	1.005	1.015	<.001
HDL (mg/dL)	1.009	0.993	1.025	.26
rGTP (U/L)	1.007	1.003	1.011	.001
AST (IU/L)	1.007	0.981	1.034	.581
ALT (IU/L)	0.985	0.970	1.001	.074

FPG, fasting plasma glucose; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; rGTP,  $\gamma$ -glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Hosmer Lemeshow goodness of fit: 11.513 df=8, P=.174; Cox and Snell R square: .205, NagelkerkeR square: .291

had an odds ratio of 1.03 for CAC, while IFG (FPG more than 100 mg/dL) had an odds ratio of 1.35. In our study, the CAC risk was associated with triglyceride and LDL-cholesterol, and this relationship was maintained after adjusting for other risk factors, including IFG. However, as compared with the odds ratio, IFG (FPG more than 110 mg/dL) had a stronger correlation with CAC in our study. Because the method of analyzing IFG was different, we could not directly compare these two studies.

Both our study and Kronmal et al found a significant correlation between smoking and CAC, but the interaction between smoking and CAC has not been fully elucidated. Some studies have shown a significant positive relationship between smoking and CAC.<sup>27,28</sup> However, other studies have also shown non-significant results. In 1999, a clinical trial from Scotland found a non-significant association between smoking and CAC.<sup>29</sup> In two other studies, a history of smoking was not significantly associated with the presence of coronary calcium in multivariable regression analyses.<sup>30,31</sup> In our study, smoking was significantly correlated with the presence of CAC in the univariate analysis, but not in the multivariate logistic analysis after adjustment for important confounders. As this study was retrospective and based on medical records, we do not have data on the number of packs of cigarettes smoked or on smoking status (former smoker vs. current smoker). Future studies will be required to confirm the dose-dependent correlation between cardiovascular risks and pack-years of exposure to smoking.

Our study has several limitations. First, there might

have been some misclassification of participants that altered the effect size associated with IFG, because FPG status was based on the results of a single blood test. We did not perform either HbA1c tests or repeated FPG tests, because subjects were enrolled from a routine health checkup. Thus, subjects with diabetes could have been included in the IFG category. However, because the study had statistically significant results in terms of finding a screening tool for CVD, this limitation is acceptable. Also, we could not fully adjust for other potentially important confounders such as physical activity, family history, or adherence to preventive recommendations, because of a lack of detailed information, which could have resulted in residual confounding. The emphasis of our study was on the importance of early detection for CVD due to increasing prevalence of CVD and other metabolic disease in an increasingly aging population.

Despite these limitations, we found that IFG (especially FPG $\geq$ 110 mg/dL) was associated with increased risk of CAC. These data suggest the importance of screening for subclinical atherosclerosis in asymptomatic patients with FPG $>$ 110 mg/dL. However, further longitudinal studies are required to determine the effect of these findings on cardiovascular events and the validity of using the FPG levels for predicting CAC.

#### **Conflict of interest and funding**

*The authors have not received any funding or benefits from industry or elsewhere to conduct this study.*

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