Association between height-corrected appendicular and regional skeletal muscle mass and insulin resistance in patients with type 2 diabetes

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Abstract. [Purpose] The effect of height-corrected skeletal muscle masses on insulin resistance has not been fully investigated in patients with type 2 diabetes. In this study, we aimed to investigate the association between height-corrected appendicular and regional skeletal muscle masses and insulin resistance in patients with type 2 diabetes. [Participants and Methods] We included 136 male and 100 female patients with type 2 diabetes (average age, male 55.7 ± 12.3 years old, female 60.7 ± 11.3 years old, and average height, male 1.67 ± 0.06 m, female 1.54 ± 0.06 m) in this study. Bioelectrical impedance analysis was used to evaluate skeletal muscle mass. We calculated the appendicular skeletal muscle mass index by dividing the appendicular skeletal muscle mass by the square of the patient’s height. The upper limb muscle mass, lower limb muscle mass, and trunk muscle mass figures were also divided by the square of the patient’s height. We used the homeostasis model assessment of insulin resistance as a marker of insulin resistance. [Results] In multiple regression analysis, the homeostasis model assessment of insulin resistance was inversely associated with appendicular skeletal muscle mass index and lower limb muscle mass/height2 in male patients with type 2 diabetes when adjusted for age and body mass index. Similarly, the homeostasis model assessment of insulin resistance was inversely associated with appendicular skeletal muscle mass index and lower limb muscle mass/height2 in non-obese female patients with type 2 diabetes. [Conclusion] We have confirmed that there is an association between appendicular skeletal muscle mass index and lower limb muscle mass/height2 with insulin resistance in male and female patients with type 2 diabetes, except in females with obesity.

Key words: Insulin resistance, Skeletal muscle mass, Type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) is characterized by a reduction in insulin secretion and an increase in insulin resistance (IR). IR is defined as an attenuated ability for insulin to generate its associated physiological responses. Insulin is an anabolic hormone that plays an important role in carbohydrate, fat, and protein metabolism by inducing glucose uptake into several cell types in the body1). Consequently, IR increases blood glucose levels, which in turn causes a reduction in skeletal muscle mass. Moreover, skeletal muscle is the primary site of insulin-stimulated glucose uptake2), and skeletal muscle mass is a major determinant of resting energy expenditure3). Furthermore, a reduction in skeletal muscle mass results in a reduction of whole body glucose uptake, which can promote the development of IR and the onset and progression of T2D. This two-way relationship between IR and skeletal muscle mass exemplifies the importance of the evaluation of skeletal muscle mass in treating and caring for T2D patients.
There are many reports that a reduction in skeletal muscle mass is associated with an increase in IR\(^1\)\(^-\)\(^8\). However, many of these studies have normalized skeletal muscle mass to body weight to investigate the association with IR. In contrast, it was reported that height-corrected skeletal muscle mass showed a positive correlation with IR. This suggests that it is necessary to consider not only the skeletal muscle mass, but also body weight when evaluating IR\(^6\),\(^7\). We also previously examined the association between whole or regional skeletal muscle mass and IR in patients with T2D\(^9\)-\(^11\). In our previous studies, the weight-corrected skeletal muscle mass showed a negative correlation with IR, whereas the height-corrected skeletal muscle mass showed a positive correlation with IR. Therefore, we concluded that the weight-corrected skeletal muscle mass was especially useful in the assessment of IR. However, the height-corrected skeletal muscle mass is a relative value indicating the ratio of skeletal muscle mass to the patient’s body weight. It is unclear whether the decrease in skeletal muscle mass was purely associated with increased IR, as the weight-corrected skeletal muscle mass decreased not only with the reductions in skeletal muscle mass, but also with the increase in body weight. Skeletal muscle mass is generally quantified using height. The Asian Working Group for Sarcopenia recommends the use of appendicular skeletal muscle mass index (ASMI) for sarcopenia evaluation\(^1\(^2\)). The negative correlation between weight-corrected skeletal muscle mass and IR indicates that body weight must be considered when examining the relationship between skeletal muscle mass and IR. The height-corrected skeletal muscle mass index does not include body weight. In our previous reports, the association between height-corrected skeletal muscle mass and IR was examined solely by simple regression analysis, without consideration of body weight. Whether the height-corrected skeletal muscle mass itself is related to IR needs to be re-verified by multiple regression analysis with consideration of body weight. If it can be verified that height-corrected skeletal muscle mass has a negative correlation with IR, it can be confirmed that an increase in skeletal muscle mass is important for alleviating IR in patients with T2D. Additionally, if the site of skeletal muscle associated with IR is clarified, resistance exercise targeting that site could be prescribed for patients with T2D. Thus, in this study, we aimed to investigate the association between height-corrected appendicular and regional skeletal muscle mass and IR among T2D patients.

**PARTICIPANTS AND METHODS**

A total of 136 male and 100 female patients with T2D who were admitted to the Center for Diabetes, Endocrinology, and Metabolism in Kansai Electric Power Hospital between November 2009 and September 2017 were included in this study (Table 1). The inclusion criteria included patients with a fasting blood glucose level of <140 mg/dL and no current treatment with insulin or oral hypoglycemic agents to properly assess IR. The study protocol was approved by the Kansai Electric Power Hospital Ethics Committee (approval number 29-141). All procedures were in accordance with the Ethical

| Variables                          | Male              | Female             |
|------------------------------------|-------------------|--------------------|
|                                    | Non-obese        | Obese              | Non-obese | Obese |
| Number                             | 67                | 69                 | 36        | 64    |
| Age (years)                        | 59.3 ± 11.5       | 52.2 ± 12.1        | 62.9 ± 9.4 | 59.6 ± 12.2 |
| Height (m)                         | 1.68 ± 0.07       | 1.68 ± 0.06        | 1.55 ± 0.07 | 1.55 ± 0.06 |
| Weight (kg)                        | 63.9 ± 7.4        | 83.4 ± 14.4        | 51.2 ± 7.3 | 72.6 ± 11.3 |
| BMI (kg/m\(^2\))                   | 22.6 ± 1.7        | 29.4 ± 3.9         | 21.4 ± 2.4 | 30.3 ± 4.2  |
| Duration of T2DM (year)            | 4.3 ± 4.5         | 3.2 ± 5.0          | 3.3 ± 7.0 | 2.5 ± 5.1 |
| HbA1c (%)                          | 7.1 ± 0.8         | 7.5 ± 1.4          | 7.3 ± 1.3 | 7.3 ± 1.2 |
| Fasting glucose level (mg/dL)      | 115.3 ± 14.4      | 108.8 ± 19.4       | 111.3 ± 16.7 | 112.4 ± 13.0 |
| Fasting insulin level (μU/mL)      | 5.1 ± 9.0         | 7.9 ± 3.8          | 4.5 ± 2.1 | 10.4 ± 5.4 |
| HOMA-IR                            | 1.20 ± 0.60       | 2.14 ± 1.02        | 1.23 ± 0.58 | 2.91 ± 1.59 |
| ASM (kg)                           | 21.4 ± 3.1        | 24.4 ± 3.4         | 14.2 ± 2.7 | 17.3 ± 2.5 |
| ASMI (kg/m\(^2\))                 | 7.57 ± 0.68       | 8.61 ± 0.75        | 5.90 ± 0.74 | 7.28 ± 0.72 |
| ULM (kg)                           | 5.4 ± 0.9         | 6.7 ± 1.1          | 3.2 ± 0.6  | 4.3 ± 0.7 |
| ULM/height\(^2\) (kg/m\(^2\))     | 1.92 ± 0.24       | 2.35 ± 0.28        | 1.33 ± 0.19 | 1.80 ± 0.24 |
| LLM (kg)                           | 16.0 ± 2.3        | 17.8 ± 2.4         | 11.0 ± 2.2 | 13.0 ± 1.9 |
| LLM/height\(^2\) (kg/m\(^2\))     | 5.65 ± 0.47       | 6.27 ± 0.52        | 4.55 ± 0.61 | 5.39 ± 0.57 |
| TM (kg)                            | 22.5 ± 2.9        | 26.1 ± 3.3         | 15.6 ± 2.2 | 19.0 ± 2.4 |
| TM/height\(^2\) (kg/m\(^2\))      | 7.96 ± 0.66       | 9.21 ± 0.79        | 6.48 ± 0.54 | 7.90 ± 0.75 |

All values are expressed as mean ± standard deviation
ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment of insulin resistance; LLM: lower limb muscle mass; TM: trunk muscle mass; T2DM: type 2 diabetes mellitus; ULM: upper limb muscle mass.

Table 1. Clinical characteristics of patients with type 2 diabetes mellitus
Guidelines for Medical and Health Research Involving Human Subjects of 2014 along with its 2017 revision, and with the updated Helsinki Declaration of 1964. Furthermore, we used an opt-out consent method based on the aforementioned ethical guidelines. Patients were informed of the objectives of the study, and permission for the investigators to collect data was sought through displayed posters in the hospital. Patients were given the opportunity to opt out of participation in the study.

The clinical data was retrospectively collected from medical records in the hospital, including baseline age, height, body weight, hemoglobin A1c level, duration of T2D, fasting glucose level, fasting insulin level, and skeletal muscle mass. Bioelectrical impedance analysis (InBody S20, InBody Japan Inc., Tokyo, Japan) was used to evaluate skeletal muscle mass. We calculated ASMI by dividing appendicular skeletal muscle mass by the square of the patient’s height. The upper limb muscle mass (ULM) and lower limb muscle mass (LLM) was calculated as the sum of the left and right limbs, respectively. The ULM, LLM, and trunk muscle mass (TM) were also divided by the square of the patient’s height. The homeostasis model assessment of IR (HOMA-IR) was used as a marker of IR. We calculated HOMA-IR by dividing the product of the fasting glucose level (mg/dL) and fasting insulin level (μU/mL) by 405. The body mass index (BMI) was also calculated by dividing the body weight by the square of the patient’s height.

All the data are presented as mean ± standard deviation. Participants were divided into a non-obese group (BMI <25 kg/m²) and an obese group (BMI ≥25 kg/m²). To examine the associations of the ASMI, ULM/height², LLM/height², and TM/height² with HOMA-IR, we performed a stepwise multiple regression analysis with age and BMI as independent variables for each sex. Statistical power and sample size were calculated using Free Statistical Calculators. Minimum required sample size was calculated to achieve the anticipated effect size of 0.35 and statistical power level of 0.8. The effect size of 0.35 was considered to be large in Free Statistical Calculators. Statistical analyses were performed using EKUSU-TOKEI 2012 for Windows (Social Survey Research Information Co., Ltd., Tokyo, Japan). Statistical significance was defined as p<0.05.

RESULTS

The relationship between the height-corrected skeletal muscle mass and HOMA-IR in multiple regression analysis is shown in Tables 2–5. ASMI and LLM/height² were inversely associated with HOMA-IR in both the non-obese and obese group of male patients with T2D when adjusted for age and BMI in the multiple regression analysis. Similarly, ASMI and LLM/height² were inversely associated with HOMA-IR in the non-obese group of female patients with T2D. However, ASMI was positively associated with HOMA-IR in the multiple regression analysis of the obese group of female patients with T2D. Additionally, the ULM/height², LLM/height², and TM/height² were not selected in the multiple regression analysis of the obese group of female patients with T2D.

Their statistical powers were 0.91 to 0.99, and minimum required sample size was 36 (Table 6).

DISCUSSION

This study clarified that ASMI was inversely associated with HOMA-IR by performing multiple regression analysis with consideration of BMI in patients with T2D. Notably, LLM/height², but not ULM/height² and TM/height², was found to be a risk factor for HOMA-IR.

A previous study reported that IR is positively associated with the height-adjusted skeletal muscle mass, but inversely associated with the weight-adjusted skeletal muscle mass, suggesting that weight-adjusted skeletal muscle mass is an ap-

| Table 2. Multiple regression analysis of skeletal muscle mass with homeostasis model assessment–insulin resistance (HOMA-IR) in non-obese group of male patients with type 2 diabetes mellitus |

| Model Independent variable | β | 95% CI Lower limit | 95% CI Upper limit | p | VIF | Adjusted R² |
|---------------------------|---|-------------------|-------------------|---|-----|----------|
| ASM                       | −0.296 | −0.493 | −0.032 | * | 1.49 | 0.25 |
| ASM                       | −0.307 | 0.131 | 0.519 | ** | 1.68 | 0.40 |
| ULM                       | −0.248 | −0.434 | 0.024 | 1.14 | 1.46 | 0.25 |
| LLM                       | −0.274 | −0.651 | −0.031 | * | 1.47 | 0.25 |
| TM                        | −0.234 | −0.512 | 0.073 | 2.12 | 0.22 |
| BMI                       | 0.588 | 0.121 | 0.343 | 2.12 | 0.22 |
| VIF Adjusted R²           | **p<0.01, p<0.05. | **p<0.01, p<0.05. | **p<0.01, p<0.05. | **p<0.01, p<0.05. | **p<0.01, p<0.05. | **p<0.01, p<0.05. |

β: standardized partial regression coefficients; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance; LLM: lower limb muscle; R²: coefficient of determination; TM: trunk muscle mass; ULM: upper limb muscle mass; VIF: variance inflation factor.
The main difference between the two measures is that the weight-adjusted skeletal muscle mass takes body weight into consideration, whereas the height-adjusted skeletal muscle mass does not. The weight-corrected skeletal muscle mass revealed a negative correlation with IR as it considers not only the skeletal muscle mass, but body weight as well. In order to examine the relationship between the height-corrected skeletal muscle mass and IR, it is suggested to consider one’s individual body weight. A multiple regression analysis was performed using BMI as a control variable. The results revealed that ASMI was independently and inversely associated with IR. Consequently, it is vital that body weight is considered in the evaluation of IR using height-corrected skeletal muscle mass.

The reason why the height-corrected skeletal muscle mass, which showed a positive correlation with IR in the single regression analysis, showed a negative correlation in the multiple regression analysis is that BMI was added as an independent variable. Not only decreased skeletal muscle mass but also increased body fat mass causes IR. Overweightness and obesity are caused by overeating and decreased physical activity, which result in the hypersecretion of insulin. Since insulin is a hormone that induces the anabolism of fat and muscle, increased insulin secretion increases body fat and skeletal muscle mass. Therefore, the increase in height-corrected skeletal muscle mass indirectly reflects the increase in body fat mass, and it is considered that a simple regression analysis showed a positive correlation with IR. The result that height-corrected

### Table 3. Multiple regression analysis of skeletal muscle mass with homeostasis model assessment-insulin resistance (HOMA-IR) in obese group of male patients with type 2 diabetes mellitus

| Model | Independent variable | β       | 95% CI Lower limit | 95% CI Upper limit | p   | VIF | Adjusted R² |
|-------|----------------------|---------|--------------------|--------------------|-----|-----|-------------|
| ASM   | ASMI                 | −0.463  | −1.063             | −0.201             | **  | 2.30| 0.26        |
|       | BMI                  | 0.784   | 0.122              | 0.286              | **  | 2.30|            |
| ULM   | ULM/height²          | −0.341  | −2.518             | 0.064              | 2.77| 0.21|            |
|       | BMI                  | 0.709   | 0.091              | 0.277              | **  | 2.77|            |
| LLM   | LLM/height²          | −0.388  | −1.314             | −0.224             | **  | 1.73| 0.26        |
|       | BMI                  | 0.688   | 0.107              | 0.250              | **  | 1.73|            |
| TM    | TM/height²           | −0.315  | −0.904             | 0.090              | 3.15| 0.20|            |
|       | BMI                  | 0.696   | 0.081              | 0.281              | **  | 3.15|            |

β: standardized partial regression coefficients; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance; LLM: lower limb muscle; R²: coefficient of determination; TM: trunk muscle mass; ULM: upper limb muscle mass; VIF: variance inflation factor.

**p<0.01, *p<0.05.

### Table 4. Multiple regression analysis of skeletal muscle mass with homeostasis model assessment-insulin resistance (HOMA-IR) in non-obese group of female patients with type 2 diabetes mellitus

| Model | Independent variable | β       | 95% CI Lower limit | 95% CI Upper limit | p   | VIF | Adjusted R² |
|-------|----------------------|---------|--------------------|--------------------|-----|-----|-------------|
| ASM   | Age                  | −0.414  | −0.046             | −0.005             | *  | 1.26| 0.30        |
|       | ASMI                 | −0.410  | −0.603             | −0.041             | *  | 1.48|            |
|       | BMI                  | 0.703   | 0.083              | 0.255              | **  | 1.48|            |
| ULM   | Age                  | −0.326  | −0.040             | −0.0003            | ** | 1.12| 0.24        |
|       | ULM/height²          | −0.286  | −1.866             | 0.150              | 1.22|    |            |
|       | BMI                  | 0.604   | 0.0630             | 0.228              | *  | 1.27|            |
| LLM   | Age                  | −0.405  | −0.046             | −0.004             | *  | 1.28| 0.27        |
|       | LLM/height²          | −0.371  | −0.696             | −0.008             | *  | 1.48|            |
|       | BMI                  | 0.678   | 0.077              | 0.250              | ** | 1.46|            |
| TM    | Age                  | −0.334  | −0.041             | −0.0006            | *  | 1.14| 0.24        |
|       | TM/height²           | −0.304  | −0.706             | 0.058              | 1.39|    |            |
|       | BMI                  | 0.646   | 0.067              | 0.244              | ** | 1.45|            |

β: standardized partial regression coefficients; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance; LLM: lower limb muscle; R²: coefficient of determination; TM: trunk muscle mass; ULM: upper limb muscle mass; VIF: variance inflation factor.

**p<0.01, *p<0.05.
skeletal muscle mass was inversely associated with IR in multiple regression analysis reaffirmed the fact that skeletal muscle mass is important for patients with T2D.

Skeletal muscle mass is generally evaluated using the whole body or total value for muscle mass and is rarely evaluated by only the ULM, LLM, or TM\(^2\). The present study has revealed the importance of assessing regional skeletal muscle mass when determining the risk of IR. LLM/height\(^2\) was found to be negatively associated with HOMA-IR through multiple regression analysis. However, ULM/height\(^2\) and TM/height\(^2\) were not associated with HOMA-IR. T2D has previously been reported to reduce skeletal muscle mass, especially LLM\(^17\). In addition, diabetic polyneuropathy has been shown to accelerate muscle atrophy in the lower legs and foot muscles\(^20\). Our results suggest that LLM is more prone to atrophy than ULM and TM in patients diagnosed with T2D. Therefore, it is possible that LLM/height\(^2\) is strongly associated with IR among skeletal muscle mass.

In this study, there was no significant difference between ULM/height\(^2\) and HOMA-IR. However, the p-value revealed trends (p-value between 0.05 and 0.10) for differences between the two measures, with the exception of the obese female group. It has been reported that ULM and LLM decrease with age for both males and females\(^23\). However, the previous study targeted elderly people between 40 and 79 years. As the average age of the participants in this study was 50 to 60 years, it

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**Table 5.** Multiple regression analysis of skeletal muscle mass with homeostasis model assessment-insulin resistance (HOMA-IR) in obese group of female patients with type 2 diabetes mellitus

| Model | Independent variable | \(\beta\) | Lower limit | Upper limit | p | VIF | Adjusted \(R^2\) |
|-------|----------------------|---------|-------------|-------------|---|-----|---------------|
| ASM   | ASMI                 | 0.301   | 0.005       | 1.335       | * | 1.69| 0.18          |
| BMI   |                      | 0.199   | -0.038      | 0.188       |   | 1.69|               |
| ULM   | Age                  | -0.219  | -0.062      | 0.005       | 1.20| 1.07|               |
| BMI   |                      | 0.302   | 0.018       | 0.209       | * | 1.20|               |
| LLM   | Age                  | -0.219  | -0.062      | 0.005       | 1.20| 1.07|               |
| BMI   |                      | 0.302   | 0.018       | 0.209       | * | 1.20|               |
| TM    | Age                  | -0.219  | -0.062      | 0.005       | 1.20| 1.07|               |
| BMI   |                      | 0.302   | 0.018       | 0.209       | * | 1.20|               |

\(\beta\): standardized partial regression coefficients; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance; LLM: lower limb muscle; \(R^2\): coefficient of determination; TM: trunk muscle mass; ULM: upper limb muscle mass; VIF: variance inflation factor.

*\(p<0.05\).

**Table 6.** Statistical calculation

| Group    | Model | Effect size | Statistical power | Minimum required sample size |
|----------|-------|-------------|-------------------|-------------------------------|
| Male     | Non-obese | ASM  | 0.37 | 0.99 | 36  |
|          |        | ULM  | 0.34 | 0.98 |     |
|          |        | LLM  | 0.37 | 0.99 |     |
|          |        | TM   | 0.31 | 0.97 |     |
|          | Obese  | ASM  | 0.39 | 0.99 |     |
|          |        | ULM  | 0.30 | 0.97 |     |
|          |        | LLM  | 0.38 | 0.99 |     |
|          |        | TM   | 0.28 | 0.96 |     |
| Female   | Non-obese | ASM  | 0.56 | 0.96 |     |
|          |        | ULM  | 0.45 | 0.91 |     |
|          |        | LLM  | 0.51 | 0.94 |     |
|          |        | TM   | 0.45 | 0.91 |     |
|          | Obese  | ASM  | 0.26 | 0.93 |     |
|          |        | ULM  | 0.24 | 0.91 |     |
|          |        | LLM  | 0.24 | 0.91 |     |
|          |        | TM   | 0.24 | 0.91 |     |

ASM: appendicular skeletal muscle mass; LLM: lower limb muscle mass; TM: trunk muscle mass; ULM: upper limb muscle mass.
was predicted that the effect of aging was small. It has also been reported that there are sexual differences in the reduction in skeletal muscle mass with aging. Specifically, ULM is less likely to decrease with age in females than in males, probably resulting in the higher p-value in females in the relationship of ULM and IR\textsuperscript{21}.

TM was not associated with IR despite having increased muscle mass when compared to LLM. It has been reported that the muscle thickness of the abdomen and subscapular also decreases with age\textsuperscript{22}. However, the muscle thickness of the abdomen decreases during one’s 40s, while the muscle thickness of the subcapular decreases during one’s 60s. Since there is a difference in the reduction in muscle thickness due to aging between the abdomen and subscapular, it is possible that the decrease in TM was associated less with IR within the participants of the current study. Another possible explanation for why TM was not shown to be associated with IR is the accuracy of the measurements recorded by the bioelectrical impedance analysis method. For the bioelectrical impedance method, a weak electric current is passed through the body and the electrical impedance is used to indirectly obtain a measurement of muscle mass. ULM and LLM consist of only skeletal muscle, whereas TM includes skeletal muscle, myocardium, and smooth muscle. Therefore, it is possible that the effect of skeletal muscle mass on IR was inaccurately shown to be reduced in the TM measurement.

There are some limitations to our study. First, this study is a cross-sectional design, so the causal relationship between skeletal muscle mass and IR was not evaluated in this study. Second, due to the small sample size, our results need to be carefully interpreted and further studies with larger sample sizes are needed to confirm our findings. Third, in this study, the bioelectrical impedance analysis method was used to measure skeletal muscle mass. The skeletal muscle mass measured by the bioelectrical impedance method may not match the actual muscle mass as there are concerns about its ability to accurately measure muscle mass. Finally, this study is a single-center study in Japan, and it is possible that our findings may not be applicable to other regions or ethnic groups.

In conclusion, we have confirmed that there is an association between reductions in ASMI and increased IR in patients with T2D, with the exception of obese females. Notably, LLM was found to be a risk factor for IR among regional skeletal muscles.

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None.

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