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Effect of statins on glycemic status and plasma adiponectin concentrations in patients with type 2 diabetes mellitus and hypercholesterolemia

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Abstract

It is reported that statins have inconsistent effects on glycemic status and adiponectin concentrations in patients with type 2 diabetes mellitus (T2DM). We aimed to investigate the effect of statins on these variables in patients with T2DM and hypercholesterolemia. A control group comprising 24 patients with T2DM but without hypercholesterolemia was observed for more than 12 weeks, while 24 patients with T2DM and hypercholesterolemia were treated with statins for the same period (statin group). The percentage changes in the glycemic status (blood glucose and glycated hemoglobin [HbA1c]), and levels of plasma adiponectin (total and high molecular weight [HMW]) were compared between the two groups. The statin group had reduced percentage changes in HbA1c, blood glucose, and total and HMW-adiponectin concentration percentage changes that were similar to those in the control group. However, when matched for sex, age (± 5 years) and HbA1c (± 0.5%) with the control group, the pravastatin group had reduced percentage changes in the plasma HMW-adiponectin concentrations than the matched controls ($p = 0.023$). However, there were no differences in the percentage changes in the plasma total adiponectin ($p = 0.137$), HbA1c ($p = 0.202$), or blood glucose concentrations ($p = 0.450$) between the two groups. Pravastatin treatment had no effect on the glycemic status of patients with T2DM and hypercholesterolemia, but may reduce the percentage changes in the plasma HMW-adiponectin concentrations. Hence, patients with T2DM and hypercholesterolemia receiving long-term treatment with pravastatin might experience increased insulin resistance.

Keywords: Statin; Pravastatin; Type 2 diabetes mellitus; Adiponectin
**Introduction**

Statins, the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are widely used in hypercholesterolemia patients, in whom they reduce the occurrence rate of cardiovascular events.\(^1\)\(^-\)\(^3\) Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular disease.\(^4\)\(^-\)\(^6\) Treatment with statins is recommended for patients with T2DM and hypercholesterolemia as they experience accelerated arteriosclerosis.\(^7\) However, the findings of several large clinical trials and meta-analyses suggest that statins may increase the incidence of new-onset T2DM.\(^8\)\(^-\)\(^10\) Statins may impair glucose metabolism. Various statins have been reported to affect glycemic status in patients with T2DM. Atorvastatin and rosuvastatin reportedly impair the glycemic status in patients with T2DM and hypercholesterolemia.\(^11\) Furthermore, a meta-analysis suggested that, in patients with T2DM, statins including atorvastatin and pravastatin are potentially associated with higher glycated hemoglobin (HbA1c) concentrations than in those without statin treatment.\(^12\) However, the results of other studies indicate that pitavastatin, pravastatin, and simvastatin do not influence the glycemic status in patients with T2DM and hypercholesterolemia.\(^13\)\(^-\)\(^15\) Thus, whether statins influence the glycemic status in patients with T2DM remains controversial.

Adiponectin is an adipokine, a hormone secreted by adipose tissue. It improves insulin sensitivity by activating AMP-activated protein kinase in the liver and skeletal muscle.\(^16\)\(^,\)\(^17\) An association between low circulating adiponectin concentrations and the development of T2DM and metabolic syndrome has been reported.\(^18\) Simvastatin reportedly reduces the plasma adiponectin concentrations and insulin sensitivity in patients with hypercholesterolemia, suggesting the mechanisms underlying the increased occurrence rates of new-onset T2DM and impairment of glucose metabolism associated with statins.\(^19\)\(^,\)\(^20\) However, pitavastatin increases the plasma adiponectin concentrations.
in patients with T2DM,\textsuperscript{21} whereas pravastatin and simvastatin do not affect plasma adiponectin concentrations.\textsuperscript{15,22} Thus, the effect of statins on circulating adiponectin concentrations is controversial.

To resolve the aforementioned issues, in the present study, we investigated the effects of statins on glycemic status and plasma adiponectin concentrations in patients with T2DM and hypercholesterolemia.

**Methods**

**Participants and design**

This prospective observational study was performed in Nagoya City University Hospital, Aichi, Japan, between September 2011 and February 2017. Patients with a diagnosis of T2DM (fasting glucose level ≥ 126 mg/dL, 2-h post-loaded glucose level ≥ 200 mg/dL, and HbA1c level ≥ 6.5%; Japan Diabetes Society) were recruited. Patients with T2DM and hypercholesterolemia who started treatment with statins were designated to the statin group. The criteria for exclusion from the statin group were as follows: 1) observation period shorter than 12 weeks; 2) statins stopped or replaced by other medications within the study period; 3) treatment for diabetes changed within the study period; 4) exercise therapy, diet therapy, or lifestyle changed within the study period; and 5) hospitalization within the study period. Patients with T2DM and without hypercholesterolemia (low-density lipoprotein (LDL)-cholesterol level ≤ 120 mg/dL; Japan Atherosclerosis Society) were designated to the control group. Sex,\textsuperscript{23} age (±5 years),\textsuperscript{23} and HbA1c (± 0.5%)\textsuperscript{24} were matched with the statin group. The criteria for exclusion from the control group included statin group exclusion criteria 1), 3), 4), and 5). At the baseline and after more than 12 weeks (the end of the study), all patients underwent a physical examination including height, weight, and body mass index (BMI) measurements.
Laboratory tests

Blood samples were obtained at the baseline and at the end of the study from Nagoya City University Hospital. The plasma concentrations of total and high molecular weight (HMW)-adiponectin were measured using an individual human adiponectin enzyme-linked immunosorbent assay kit (Otsuka Pharmaceutical, Tokyo, Japan) in accordance with the instruction manual. Other data were obtained from medical record.

Matching between patients receiving pravastatin treatment and the control group

Sex, age, and HbA1c were matched between patients receiving pravastatin treatment only (n = 15) (the remaining 9 that were not included received fluvastatin, rosuvastatin, and atorvastatin) and the control patients, as these variables are reportedly relevant to circulating adiponectin concentrations.

Statistical analysis

We conducted this study with percentage changes in plasma HMW-adiponectin concentrations as the primary endpoint and percentage changes in plasma total adiponectin concentrations as the secondary endpoint, during the study period. All results are presented as mean (25th, 50th [median], 75th percentile [interquartile ranges]) or mean ± standard deviation, with n values representing the number of patients. Intergroup differences were analyzed by unpaired t-tests (normally distributed variables) or a Mann–Whitney U test (non-normally distributed variables). Intergroup differences using the matching method were analyzed by paired t-tests (normally distributed variables) or a Wilcoxon signed rank test (non-normally distributed variables). Differences in the proportion of the sexes in each group were analyzed by a $\chi^2$ test. A value of $p < 0.05$ was
indicative of statistical significance. All statistical analyses were performed using SPSS Statistics 18.0 (SPSS, IL, Chicago, IL, USA).

Human rights statement and informed consent
All procedures followed were in accordance with the ethical standards of the Nagoya City University Hospital Clinical Research Review board (Nagoya City University Graduate School of Medical Science; date of approval: May 10, 2011; approval number: 559) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before study inclusion.

Results
Flow chart of participant selection
Of the 62 patients initially enrolled in the control group during the survey period, 29 were excluded: because they met the exclusion criteria (26 patients), had missing blood sample (2) and weight (1) data. In addition, 9 of the patients in the control group were lost during the follow-up. Thus, 24 patients were included in the study analyses of the control group (Fig. 1). Of the 46 patients initially enrolled in the statin group during the survey period, 18 were excluded: 9 because they met the exclusion criteria, 4 had missing blood samples, 2 discontinued with statins use, and 3 experienced adverse events (2 developed myalgia that was considered related to statins and 1 had abdominal pain that was considered possibly related to statin use.). A further 4 patients were lost to follow-up. Thus, 24 patients were included in the study analyses of the statin group (Fig. 1).

Participants’ baseline characteristics and clinical variables
The baseline characteristics of all the participants are presented in Table 1. The mean
patient age, sex, estimated duration of diabetes, and observation period were similar between the control and statin groups. Patients in the statin group were treated with pravastatin (n = 15), fluvastatin (n = 4), rosuvastatin (n = 4), and atorvastatin (n = 1). Patients were treated with seven categories of diabetes medication. Of these seven categories, insulin and sulfonylurea were used more often in the control than the statin group. The relevant baseline clinical and laboratory findings of all the participants are presented in Table 2. The baseline BMI, plasma lipid variable (triglyceride, and total, HDL- and LDL-cholesterol), glycemic status variable (blood glucose and HbA1c), and plasma adiponectin (total and HMW) values were similar between the two groups.

Changes in the clinical variables in all participants
The percentage changes in the total and LDL-cholesterol levels were reduced in the statin group compared to the control group. The percentage changes in the triglyceride, HDL-cholesterol, HbA1c, blood glucose, and plasma total and HMW-adiponectin concentrations did not differ significantly between the control and statin groups (Table 3). Plasma total and HMW-adiponectin concentrations did not significantly change between baseline and the end of the study in the control and the statin groups (Figs. 2. A, B).

Baseline characteristics and clinical variables in the matched patients
Eleven pairs were created by matching sex, age, and HbA1c. The baseline characteristics of the matched patients are presented in Table 4. The mean patient age, sex, estimated duration of diabetes, and observation period were similar between the matched control and pravastatin groups. The diabetes medications administered did not differ between the two groups. The baseline clinical and laboratory characteristics of the matched patients are presented in Table 5. The BMI, triglyceride, total, HDL- and LDL-cholesterol, blood
glucose, plasma total, and HMW-adiponectin values were similar between the two matched groups; however, the HbA1c level differed between them. As 4 of the 11 pairs had the same values and the interquartile ranges were identical in the two matched groups. It was considered that the difference in the HbA1c values would have a negligible influence on the results of the comparison of the changes in all the assessed variables between the two matched groups.

Changes in the laboratory variables in the matched patients
The percentage changes in the total and LDL-cholesterol and plasma HMW-adiponectin concentrations were reduced in the pravastatin group compared to the matched control group, while the percentage changes in the triglyceride, HDL-cholesterol, HbA1c, blood glucose, and plasma total adiponectin concentrations did not differ significantly between the matched control and pravastatin groups (Table 6). In addition, plasma total adiponectin concentrations did not change significantly between baseline and the end of the study. However, its concentrations tend to indicate a reduction. On the other hand, plasma HMW-adiponectin concentrations were significantly reduced by the end of the study compared with baseline, in the pravastatin group (Figs. 2. C, D).

Discussion
In the present study, we investigated how statin treatment affected plasma adiponectin concentrations in patients with T2DM and hypercholesterolemia. We found that pravastatin treatment was associated with significantly lower plasma HMW-adiponectin concentrations in patients with T2DM and hypercholesterolemia than in those without hypercholesterolemia (pravastatin untreated patients). This is the first study to our knowledge to report the effect of pravastatin on reduction of plasma HMW-adiponectin
concentrations with T2DM.

Though few patients with T2DM were started on statin therapy at Nagoya City University Hospital, in only a small number of patient were recruited into the statin group during the survey period, ultimately the number of participants who completed the study were the same in both groups. Furthermore, we employed matched-pair analyses, a method frequently used in clinical trials, and created closely approximated pairs among the control and statin groups using sex, age, and HbA1c.

Adiponectin, a hormone secreted by adipose tissue, has antidiabetic, anti-arteriosclerotic, and anti-inflammatory properties. Reduction in the blood adiponectin concentrations is one mechanism by which statin treatment can result in increased blood glucose concentrations. Plasma adiponectin has three oligomeric forms: a trimer (low molecular weight), hexamer (medium molecular weight), and large oligomer of 12–18 subunits (HMW)(the most bioactive of the three, which is the most strongly associated with insulin sensitivity). The sex, age, and HbA1c are effective factors of adiponectin concentrations. In this study, the plasma HMW-adiponectin concentrations, but not the total adiponectin concentrations, were lower in patients with T2DM and hypercholesterolemia receiving pravastatin than in their sex- and HbA1c-matched counterparts in the control group, not receiving statins. Previous studies have reported an association between pravastatin treatment and increases in the plasma total adiponectin concentrations in patients with hypercholesterolemia, impaired glucose tolerance, and coronary artery disease. However, our findings on the effects of pravastatin treatment on plasma total adiponectin concentrations in patients with T2DM and hypercholesterolemia are consistent with those of previous studies, showing that treatment with pravastatin does not change serum total adiponectin concentrations.

In contrast, pravastatin treatment reportedly increases the serum HMW-adiponectin
concentrations in patients with coronary artery disease\textsuperscript{28} but does not, in patients with hypercholesterolemia\textsuperscript{29}. In a previously cited study, 20 mg or 40 mg 16-week pravastatin treatment had no effect on the serum HMW-adiponectin concentrations of patients with T2DM and hypercholesterolemia\textsuperscript{22}. Due to these conflicting findings, it was suggested that the effect of pravastatin treatment on circulating total and HMW-adiponectin concentrations may differ according to various patient characteristics and, in particular, may be weak in patients with T2DM\textsuperscript{22}.

In this study, pravastatin treatment reduced the plasma HMW-adiponectin concentrations in T2DM patients with hypercholesterolemia; however, this treatment did not change the glycemic status. One proposed mechanism for the deterioration in the glucose metabolism caused by statins is that statins may impair the secretion of insulin by pancreatic β cells by having direct and indirect effects on calcium channels\textsuperscript{20}. Simvastatin reportedly inhibits insulin secretion via blocked L-type calcium channels in rat pancreatic β cells, whereas pravastatin does not\textsuperscript{30}. Additionally, it has been reported that pravastatin treatment improves β cell function in patients with early T2DM and hypercholesterolemia\textsuperscript{27}. The reduction in insulin sensitivity in the liver and adipocytes associated with decreases in the plasma HMW-adiponectin concentration is likely associated with pravastatin-related increased insulin secretion by pancreatic β cells; therefore, pravastatin use might not have increased the blood glucose concentrations in patients with T2DM and hypercholesterolemia. However, it was suggested that reductions in the plasma HMW-adiponectin concentrations increase insulin resistance\textsuperscript{25}. Therefore, when pravastatin is administered long-term to patients with T2DM, it may be necessary to monitor for glycemic status deteriorations.

The most relevant of this study’s limitations is the small sample size. However, it is remarkable that pravastatin treatment, which is reported to have little effect on glycemic
status, 14,31,32) decreased the plasma HMW-adiponectin concentrations in patients with T2DM. In addition, conducting clinical experiments supersede animal experiments, even when the sample size is small. Secondly, pravastatin treatment did not affect glycemic status, probably because of the short duration of observation. Thirdly, the medications for diabetes were not matched between the groups. However, as these medications were not changed during this study, we believe that this did not have a large impact on the results of the study. Analysis of the effects of pravastatin treatment on glycemic status and plasma adiponectin concentrations in T2DM patients requires further large-size, long-term studies that address the medications used to treat diabetes in the groups.

Conclusions

Twelve weeks of treatment with pravastatin did not affect glycemic status, but was associated with significant decrease in the plasma HMW-adiponectin concentrations in patients with T2DM and hypercholesterolemia. Patients with T2DM and hypercholesterolemia receiving long-term treatment with pravastatin might experience increased insulin resistance.
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Conflict of interest statement

The authors declare that they have no conflicts of interest associated with this study.
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**Figure legend**

**Fig. 1.** Flow diagram of participant inclusion.

**Fig. 2.** Changes in the adiponectin concentrations in all participants and the matched patients.

Data are mean ± standard deviation, Numbers of patient in control group = 24, Numbers of patient in statin group = 24, Numbers of patient in matched control group = 11, Numbers of patient in pravastatin group = 11. HMW-adiponectin, high molecular weight-adiponectin.
Fig.1 Hori et al.

Control Group
- Enrolled, 62 patients
- Study completed, 24 patients
- Study discontinuations:
  - 9 did not meet the inclusion criteria or met the exclusion criteria
  - 4 missing blood samples
  - 3 adverse events
  - 2 discontinued taking statin
  - 4 patients interrupted visits

Statin Group
- Enrolled, 46 patients
- Study completed, 24 patients
- Study discontinuations:
  - 26 did not meet the inclusion criteria or met the exclusion criteria
  - 2 missing blood samples
  - 1 missing weight data
  - 9 patients interrupted visits
  - 1 missing weight data
  - 9 patients interrupted visits
Fig. 2 Hori et al.

A. **All participants**

- **Total adipnectin (µg/mL)**
  - Baseline: Control: 20, Statin: 18
  - End point: Control: 16, Statin: 14
  - p = 0.484 (baseline), p = 0.094 (end point)

B. **All participants**

- **HMW-adipnectin (µg/mL)**
  - Baseline: Control: 10, Statin: 9
  - End point: Control: 8, Statin: 7
  - p = 0.070 (baseline), p = 0.846 (end point)

C. **Matched patients**

- **Total adipnectin (µg/mL)**
  - Baseline: Matched Control: 22, Pravastatin: 20
  - End point: Matched Control: 18, Pravastatin: 16
  - p = 0.891 (baseline), p = 0.050 (end point)

D. **Matched patients**

- **HMW-adipnectin (µg/mL)**
  - Baseline: Matched Control: 10, Pravastatin: 9
  - End point: Matched Control: 8, Pravastatin: 7
  - p = 0.759 (baseline), p = 0.016 (end point)
Table 1. Relevant baseline characteristics according to study group

|                              | Control (n = 24) | Statin (n = 24) | P value |
|------------------------------|------------------|-----------------|---------|
| Age (years)                  | 67 (64, 66, 74)  | 62 (57, 62, 71) | 0.081   |
| Gender (male/female)         | 14 / 10          | 10 / 14         | 0.248   |
| Estimated diabetic duration (years) | 8.4 (5.3, 8.0, 12.0) | 6.0 (1.8, 3.5, 9.0) | 0.066   |
| Observation period (weeks)   | 16 (14, 15, 16)  | 16 (13, 16, 19) | 0.546   |
| Use of statins               |                  |                 |         |
| Pravastatin                  | -                | 15              |         |
| Fluvastatin                  | -                | 4               |         |
| Rosuvastatin                 | -                | 4               |         |
| Atorvastatin                 | -                | 1               |         |
| Treatment of diabetes        |                  |                 |         |
| DPP4 inhibitor               | 15               | 13              |         |
| Sulfonylurea                 | 12               | 5               |         |
| Alpha-glucosidase inhibitor  | 9                | 7               |         |
| Metformin                    | 8                | 11              |         |
| Insulin                      | 7                | 3               |         |
| Pioglitazone                 | 1                | 4               |         |
| Glinide                       | 1                | 0               |         |

(n) indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). DPP4, dipeptidyl-peptidase 4.
Table 2. Relevant baseline clinical and laboratory findings according to study group

|                      | Control (n = 24) | Statin (n = 24) | P value |
|----------------------|-----------------|----------------|---------|
| BMI (kg/m²)          | 22.5 (20.3, 22.9, 23.9) | 24.6 (21.7, 24.6, 27.4) | 0.065   |
| Triglyceride (mg/dL) | 135 (88, 126, 166) | 137 (96, 129, 171) | 0.917   |
| Total cholesterol (mg/dL) | 179 (161, 181, 198) | 252 (233, 252, 268) | < 0.001 |
| HDL-cholesterol (mg/dL) | 62 (45, 58, 77) | 61 (51, 59, 67) | 0.934   |
| LDL-cholesterol (mg/dL) | 89 (78, 90, 100) | 163 (150, 161, 178) | < 0.001 |
| Blood glucose (mg/dL) | 150 (124, 134, 175) | 146 (113, 131, 162) | 0.543   |
| HbA1c (%)            | 6.9 (6.5, 6.9, 7.2) | 7.1 (6.5, 7.1, 7.7) | 0.319   |
| Total adiponectin (µg/mL) | 12.7 (7.3, 10.9, 15.3) | 12.7 (6.8, 9.8, 16.3) | 0.726   |
| HMW-adiponectin (µg/mL) | 7.7 (3.5, 5.0, 9.9) | 9.3 (3.4, 6.7, 11.3) | 0.711   |

(n) indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). BMI, body mass index; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; HMW-adiponectin, high molecular weight-adiponectin.
### Table 3. Percentage changes in clinical and laboratory variables according to study group

|                          | Control (n = 24) | Statin (n = 24) | P value |
|--------------------------|-----------------|-----------------|---------|
| Triglyceride             | 9.7             | 8.9             | 0.893   |
|                         | (-20.2, 7.5, 30.8) | (-17.1, 5.0, 23.4) |         |
| Total cholesterol        | 5.6             | -21.7           | < 0.001 |
|                         | (-0.3, 3.8, 10.9) | (-29.7, -16.9, -14.9) |       |
| HDL-cholesterol         | -0.2            | -3.0            | 0.434   |
|                         | (-8.0, 0.8, 6.8) | (-13.2, -3.6, 5.1) |       |
| LDL-cholesterol         | 10.9            | -33.1           | < 0.001 |
|                         | (-0.8, 7.5, 25.6) | (-43.4, -32.3, -22.7) |       |
| Blood glucose           | -0.8            | 2.6             | 0.650   |
|                         | (-24.7, -3.7, 13.9) | (-21.1, 4.4, 16.3) |       |
| HbA1c                   | 1.4             | 0.5             | 0.695   |
|                         | (-3.0, 0.0, 5.1) | (-1.7, 1.5, 4.7) |       |
| Total adiponectin       | 1.2             | -4.9            | 0.331   |
|                         | (-12.2, 3.2, 11.8) | (-17.9, -8.4, 10.1) |       |
| HMW-adiponectin         | 0.8             | -5.8            | 0.155   |
|                         | (-12.0, -2.8, 20.8) | (-22.1, -13.4, 5.9) |       |

*(n) indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; HMW-adiponectin, high molecular weight-adiponectin.*
Table 4. Relevant baseline characteristics in matched control and pravastatin groups

|                        | Matched Control  | Pravastatin  | P value |
|------------------------|------------------|--------------|---------|
|                        | \( n = 11 \)     | \( n = 11 \) |         |
| Age (years)            | 68 (63, 68, 75)  | 66 (61, 64, 74) | 0.094   |
| Estimated diabetic duration (years) | 8.1 (4.0, 7.0, 12.0) | 5.3 (1.5, 3.0, 5.5) | 0.181   |
| Observation period (weeks) | 16 (14, 16, 18)  | 18 (16, 19, 20) | 0.145   |
| Treatment of diabetes  |                  |              |         |
| DPP4 inhibitor         | 7                | 5            | -       |
| Sulfonylurea           | 3                | 1            | -       |
| Alpha-glucosidase inhibitor | 3            | 4            | -       |
| Metformin              | 3                | 4            | -       |
| Insulin                | 4                | 2            | -       |
| Pioglitazone           | 0                | 1            | -       |
| Glinide                | 1                | 0            | -       |

\( (n) \) indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). DPP4, dipeptidyl-peptidase 4.
Table 5. Relevant baseline clinical and laboratory variables in matched control and pravastatin groups

|                        | Matched Control ($n = 11$) | Pravastatin ($n = 11$) | P value |
|------------------------|----------------------------|------------------------|---------|
| BMI (kg/m$^2$)         | 21.4 (19.3, 21.4, 23.2)    | 24.1 (22.5, 23.2, 26.2) | 0.081   |
| Triglyceride (mg/dL)   | 123 (95, 121, 145)         | 159 (127, 150, 207)    | 0.241   |
| Total cholesterol (mg/dL) | 182 (171, 183, 201)     | 253 (236, 252, 270)    | < 0.001 |
| HDL-cholesterol (mg/dL) | 65 (49, 61, 80)            | 62 (55, 59, 62)        | 0.534   |
| LDL-cholesterol (mg/dL) | 93 (83, 95, 105)           | 159 (151, 162, 167)    | < 0.001 |
| Blood glucose (mg/dL)  | 126 (111, 127, 130)        | 132 (108, 123, 143)    | 0.476   |
| HbA1c (%)              | 6.6 (6.4, 6.5, 7.0)        | 6.7 (6.4, 6.7, 7.0)    | 0.038   |
| Total adiponectin (µg/mL) | 13.9 (8.1, 11.8, 18.4)    | 12.4 (6.6, 9.2, 16.6)  | 0.534   |
| HMW-adiponectin (µg/mL) | 9.2 (3.7, 8.1, 13.6)      | 9.0 (3.4, 5.3, 10.5)   | 0.790   |

($n$) indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). BMI, body mass index; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; HMW-adiponectin, high molecular weight-adiponectin.
Table 6. Percentage changes in clinical and laboratory variables in matched control and pravastatin groups

|                          | Matched Control $(n = 11)$ | Pravastatin $(n = 11)$ | P value |
|--------------------------|-----------------------------|------------------------|---------|
| Triglyceride             | 15.9 (0.4, 8.0, 22.7)       | 12.3 (-19.8, 0.6, 25.4) | 0.286   |
| Total cholesterol        | 7.9 (-1.4, 4.2, 14.1)       | -18.7 (-22.3, -15.9, -13.3) | < 0.001 |
| HDL-cholesterol          | 0.5 (-5.9, 0.0, 6.5)        | -4.7 (-15.7, -8.5, 7.2)  | 0.413   |
| LDL-cholesterol          | 12.0 (0.5, 5.1, 27.6)       | -30.7 (-38.4, -33.3, -18.4) | < 0.001 |
| Blood glucose            | 1.8 (-16.7, -6.6, -9.7)     | 12.6 (-3.9, 10.9, 16.9)  | 0.450   |
| HbA1c                    | 1.3 (-3.2, 0.0, 2.9)        | 2.8 (0.6, 3.0, 4.8)      | 0.202   |
| Total adiponectin        | 4.4 (-7.0, 3.1, 17.1)       | -10.2 (-18.9, -13.5, -5.5) | 0.137   |
| HMW-adiponectin          | 5.6 (-12.2, 0.1, 23.9)      | -19.0 (-31.1, -21.3, -12.3) | 0.023   |

$(n)$ indicates the number of patients. Values are presented as mean (25th, 50th [median], 75th percentiles [interquartile ranges]). HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; HbA1c, glycated hemoglobin A1c; HMW-adiponectin, high molecular weight-adiponectin.