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Improvement of Glycemic Control by Re-education in Insulin Injection Technique in Patients with Diabetes Mellitus --Manuscript Draft--

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Abstract:	<p>Introduction: The aim of this study was to evaluate the effectiveness of re-education in the insulin injection technique for glycemic control.</p> <p>Methods: A preliminary experimental study was performed with 87 insulin-treated diabetic outpatients (11 with type 1 diabetes, 76 with type 2 diabetes; 43 men, 44 women). All patients had been treated with insulin for more than 3 years. After answering questions about the insulin injection technique, the patients' knowledge levels were scored. Correct answers and explanation sheets were subsequently given to all patients. The physicians in charge gave a short lecture and provided 10 minutes of individual advice. Two, three, and four months after re-education the HbA1c and glycoalbumin levels were measured.</p> <p>Results: The mean HbA1c levels of almost all patients significantly improved from $7.46 \pm 0.09\%$ to $6.73 \pm 0.10\%$ ($P < 0.01$), and the mean glycoalbumin levels significantly improved from $22.76 \pm 0.50\%$ to $20.26 \pm 0.68\%$ ($P < 0.01$). Twenty-five patients demonstrated a poor understanding (score of ≤ 6 points) and showed a significant decrease in the HbA1c level from $7.62 \pm 0.20\%$ to $6.71 \pm 0.21\%$ ($P = 0.02$). Forty-three patients demonstrated a moderate understanding (score of 7 or 8 points) and showed a decrease in the HbA1c level from $7.40 \pm 0.13\%$ to $6.68 \pm 0.07\%$ ($P = 0.07$). Finally, 19 patients demonstrated a good understanding (score of ≥ 9 points) and showed a slight decrease in the HbA1c level from $7.38 \pm 0.15\%$ to $6.93 \pm 0.12\%$ ($P = 0.09$). Patients with a poor understanding showed the largest decrease in the mean level of HbA1c.</p> <p>Conclusion: Re-education in the insulin injection technique led to an improvement in glycemic control in insulin-treated diabetic patients, especially in those with a poor understanding of the insulin injection technique. More attention should be paid to these strategies for outpatients.</p>
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ORIGINAL RESEARCH

Improvement of Glycemic Control by Re-education in Insulin Injection Technique in Patients with Diabetes Mellitus

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ABSTRACT

Introduction: The aim of this study was to evaluate the effectiveness of re-education in the insulin injection technique for glycemic control.

Methods: A preliminary experimental study was performed with 87 insulin-treated diabetic outpatients (11 with type 1 diabetes, 76 with type 2 diabetes; 43 men, 44 women). All patients had been treated with insulin for more than 3 years. After answering questions about the insulin injection technique, the patients' knowledge levels were scored. Correct answers and explanation sheets were subsequently given to all patients. The physicians in charge gave a short lecture and provided 10 minutes of individual advice. Two, three, and four months after re-education the HbA_{1c} and glycoalbumin levels were measured.

Results: The mean HbA_{1c} levels of almost all patients significantly improved from $7.46 \pm 0.09\%$ to $6.73 \pm 0.10\%$ ($P < 0.01$), and the mean glycoalbumin levels significantly improved from $22.76 \pm 0.50\%$ to $20.26 \pm 0.68\%$ ($P < 0.01$). Twenty-five patients demonstrated a poor understanding (score of ≤ 6 points) and showed a significant decrease in the HbA_{1c} level from $7.62 \pm 0.20\%$ to $6.71 \pm 0.21\%$ ($P = 0.02$). Forty-three patients demonstrated a moderate understanding (score of 7 or 8 points) and showed a decrease in the HbA_{1c} level from $7.40 \pm 0.13\%$ to $6.68 \pm 0.07\%$ ($P = 0.07$). Finally, 19 patients demonstrated a good understanding (score of ≥ 9 points) and showed a slight decrease in the HbA_{1c} level from $7.38 \pm 0.15\%$ to $6.93 \pm 0.12\%$ ($P = 0.09$). Patients with a poor understanding showed the largest

decrease in the mean level of HbA1c.

Conclusion: Re-education in the insulin injection technique led to an improvement in glycemic control in insulin-treated diabetic patients, especially in those with a poor understanding of the insulin injection technique. More attention should be paid to these strategies for outpatients.

Keywords: diabetes mellitus; glycemic control; insulin; insulin injection technique; re-education

INTRODUCTION

Glycemic control through insulin treatment is appropriate for both type 1 and type 2 diabetes if control through oral therapy is inadequate or internal insulin secretion has decreased [1]. In particular, severe glycemic control through intensive insulin treatment (three or more daily insulin treatment) has been shown to lower the occurrence/progress of complications in diabetic patients [2, 3].

At present, approximately 700,000–800,000 of 8.9 million diabetic patients in Japan are receiving insulin treatment [4]. About 4 million people in the United States and about 3.8 million people in Europe are using insulin, and the number of such patients continues to increase [5].

The development of insulin preparations and injectors has contributed significantly to the progress in insulin treatment, and pen-type insulin injectors are now common [6]. The convenience and ease of use of injectors has improved dramatically, and the introduction of outpatient insulin treatment is actively being promoted [7].

However, the act of injecting oneself with drugs is not a normal activity for many patients and can thus cause anxiety. Furthermore, instruction in self-injection is often only given at the start of insulin treatment and often patients cannot understand how to self-inject insulin perfectly [8]. Recently, there has been an emergence of many patients with a long history of insulin treatment, as well as many elderly patients, and continuous instruction is

needed [9]. Therefore, it is important that medical staff give step-by-step instructions on the key points of the injection technique and confirm that the patient has understood the instructions correctly [10].

In addition, when self-injection of insulin is conducted at home, glycemic control can fluctuate because of various factors related to daily life [11]. A high self-management capability is thus required to maintain favorable glycemic control. To that end, appropriate clinical instruction suited to individual characteristics is needed. Patients who conduct self-injections of insulin under self-management must be knowledgeable in the reasons behind problems associated with glycemic control.

Therefore, this study evaluated outpatients at the Dokkyo Medical University Hospital performing self-injections of insulin and investigated the degree of individual understanding of injection techniques. Re-education was then conducted with an emphasis on points that were poorly understood and techniques that were prone to mistakes or omissions. The impact of this re-education on glycemic control was then studied.

METHODS

Study Population

This study included 87 outpatients with diabetes performing self-injections of insulin and treated at a single outpatient clinic (Dokkyo Medical University Hospital, Tochigi, Japan).

Patients were included in the study if they had been treated with insulin for more than 3 years, and could administer insulin injection by themselves. They used 31-G needle before this study and didn't change the needle. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study. Patients glycemic levels were monitored for any adverse events (e.g. problems with glycemic control) and insulin levels were adjusted as necessary.

Study Design

Techniques for self-injection of insulin were confirmed using a questionnaire (Figure 1), and re-education in insulin injection techniques was conducted once a month using an educational manual (Figure 2). The nine items related to the insulin self-injection technique are described as follows.

Any air present in the insulin cartridge should be removed. The presence of a large amount of air inside the cartridge reportedly prevents an appropriate amount of insulin from being injected [12]. A study in Japan reported that the smaller the amount of air mixed in the cartridge, the better the accuracy of the injector [12]. In addition, storing the injector with the needle still attached results in the entrance of air from the needle tip and an increase in the number of air bubbles over time; thus, needles must be detached immediately after use.

Freezing and thawing of unused insulin preparations can also cause the formation of air bubbles, in which case an air bubble is generated due to the temperature change. Therefore, patients were instructed to ensure that unused insulin preparations were not frozen and were instead kept refrigerated at 2 to 8°C [13]. In addition, in cloudy insulin preparations, the introduction of air has reportedly changed the concentration of the insulin [14].

A trial injection should be performed. A trial injection is necessary to let air bubbles out of the cartridge and the equipped needle. This is also an important step for confirming that the needle is installed properly and that the injector works properly.

Insulin should be injected into the abdomen. Subcutaneous injection into the abdomen is most common because absorption of insulin is quick [15], it is least affected by exercise [16, 17] and outside temperature [18-20], and it is less painful compared with other sites [7]. It has also been pointed out that injecting into the abdomen lessens blood glucose fluctuations [21].

The stiffness of the injection area should be checked. Stiffness in the area where insulin is injected is the result of expansion of fat tissue, and it often occurs when injections are repeated in the same area. This not only promotes fat synthesis in the insulin-injected area, but has also been observed to involve the immune system [22]. When an injection is made into an area with expanded fat tissue, the injection is less painful, but a delay occurs in insulin absorption; thus, the effect of the insulin is not fully manifested [23]. We advised patients to

inject into the same location every time and to avoid skin abnormalities by changing locations by 2 to 3 cm. Because frequent insulin injections have become common, there have been reports that approximately half of patients with type 1 diabetes experience stiffness [24], that HbA_{1c} levels are significantly higher in these patients than in patients without stiffness [25], and that HbA_{1c} levels improve by changing the location of injections [22].

The skin should be pinched while injecting. The skin structure of human beings comprises the epidermis, dermis, hypodermis, and musculature. Because the epidermis and dermis contain many immune, nerve, and lymph cells, an intradermal injection of insulin may stimulate nerve endings and increase pain or result in an increased immune response to the insulin [26]. An intramuscular injection will double the rate of insulin absorption [27]. Conversely, the hypodermis comprises mostly fat and is well suited for insulin injections. Some thin patients have almost no subcutaneous fat at all, and we instructed such patients to pinch the skin while injecting to ensure stable absorption.

The injection should be at a straight angle. If the angle of the injection is not perpendicular to the skin, the insulin may be intradermally injected [28]. We instructed patients to perform a perpendicular injection.

The injection button should be pressed in gently. Some time is required for the insulin to completely flow into the injected area. We instructed patients to inject by calmly and gently pushing in.

The needle should be pulled out slowly. As the diameter of the injector needle decreases, injection resistance increases and the time required for insulin to flow into the site lengthens [29]. For complete inflow of insulin, the patient must wait for a certain period of time after pushing the injector button, and it is important that insulin does not leak from the needle tip after pulling the needle out. Because a thin 31-G needle was used for this study, we instructed patients to wait for 15 seconds after pushing the injector button.

The needle should be pulled out while the injection button is held down. Continuing to push the injector button whilst pulling the needle out will prevent blood from mixing with the insulin (so-called reflux). The most likely reason for reflux is releasing the finger from the injector button before pulling the needle out, which lowers the pressure inside the cartridge [30].

We didn't re-educate a change in diet or the rate of self-glucose monitoring during this study period. We also believe that it shows more accurate educational effect by using two indices, HbA_{1c} and glycoalbumin.

HbA_{1c} and glycoalbumin levels were used as glycemic control indices. These were measured before and 2, 3, and 4 months after re-education. HbA_{1c} was measured using a Determiner HbA_{1c} Kit[®] (Kyowa Medex Co., Ltd., Tokyo, Japan), and glycoalbumin was measured using a Lucica GA-L Kit[®] (Asahi Kasei Pharma Co., Ltd., Tokyo, Japan). During

this period, insulin units were not changed with the exception of frequent low glycemic levels and severely high glycemic levels.

Of the insulin self-injection techniques, nine items were scored (Figure 1). These scores were totaled, and a dispersion chart was produced according to the scores. The dispersion chart was divided into three groups (Figure 3), and changes in the HbA_{1c} level was observed for each group.

Statistical Analysis

The results are presented as mean \pm SE. Comparisons of two groups were made using the unpaired *t* test for continuous variables. Two-tailed *P* values of <0.05 were considered statistically significant. All data were analyzed using JMP7 (SAS Institute Inc., NC, USA).

RESULTS

Clinical Characteristics of the Subjects

Eighty-seven patients with diabetes were enrolled in the study. Patient characteristics are shown in Table 1. The breakdown of the number of daily insulin injections is shown in Table 1.

HbA_{1c} and Glycoalbumin Levels for all groups

The mean HbA_{1c} level the start of re-education was $7.46 \pm 0.09\%$. The level significantly decreased to $7.11 \pm 0.09\%$ ($P < 0.01$) 2 months after re-education, to $7.05 \pm 0.11\%$ ($P < 0.01$) 3

months after re-education, and to $6.73 \pm 0.10\%$ ($P < 0.01$) 4 months after re-education.

The mean glycoalbumin level before re-education was $22.76 \pm 0.50\%$. The level significantly decreased to $21.85 \pm 0.41\%$ ($P < 0.01$) 2 months after re-education, to $21.28 \pm 0.56\%$ ($P < 0.01$) 3 months after re-education, and to $20.26 \pm 0.68\%$ ($P < 0.01$) 4 months after re-education (Figure 4).

During this 4 month period, 11 patients' insulin units were decreased because of low glycemic levels, and two patients' insulin units were increased because of problems with glycemic control.

HbA_{1c} and Glycoalbumin Levels by Group

The breakdown of the total scores for the nine items related to self-injection techniques was as follows: 7 patients with 4 points, 6 with 5 points, 12 with 6 points, 23 with 7 points, 20 with 8 points, 11 with 9 points, and 8 with 10 points. The 25 patients with 4 to 6 points were classified as Group I (poor understanding), the 43 patients with 7 or 8 points were classified as Group II (moderate understanding), and the 19 patients with 9 or 10 points were classified as Group III (good understanding; Figure 3).

The mean HbA_{1c} level in Group I was $7.62 \pm 0.20\%$ the start of re-education and showed significant improvement to $7.37 \pm 0.18\%$ ($P < 0.01$) 2 months after re-education, to $7.25 \pm 0.18\%$ ($P < 0.05$) 3 months after re-education, and to $6.71 \pm 0.21\%$ ($P < 0.05$) 4 months after re-education.

The mean HbA_{1c} level in Group II decreased from 7.40±0.13% before re-education to 6.87±0.10% ($P < 0.01$) 2 months after re-education, to 6.90±0.18% ($P < 0.06$) 3 months after re-education, and to 6.68±0.12% ($P = 0.07$) 4 months after re-education. A significant decrease was only observed 2 months after re-education.

The mean HbA_{1c} level in Group III decreased from 7.38±0.15% at the start of re-education to 7.36±0.17% ($P = 0.63$) 2 months after re-education, to 7.35±0.30% ($P = 0.81$) 3 months after re-education, and to 6.93±0.17% ($P = 0.09$) 4 months after re-education. A downward trend was shown, but none of the changes were statistically significant (Figure 5).

DISCUSSION

In this study, re-education in insulin self-injection techniques was performed once a month for approximately 4 months. HbA_{1c} and glycoalbumin levels decreased significantly as a result of re-education. Patients with a poor understanding of self-injection techniques had high levels of HbA_{1c} prior to re-education. Furthermore, patients with a poor understanding of self-injection techniques had a greater rate of decrease in the HbA_{1c} level as a result of re-education. A correlation reportedly exists between knowledge of diabetes and HbA_{1c} levels when education/instruction on diabetes is instituted over a long period of time [31]. Similarly, the present study indicated that repeated instruction in insulin self-injection techniques has a favorable effect on glycemic control.

This study has certain limitations. This study did not have a control group because it used all outpatients who matched the inclusion criteria at the Dokkyo Medical University Hospital. We know that often a patient's behavior is changed by result of re-education. Therefore, we didn't re-educate change in diet, exercise, and the rate of self-glucose monitoring during this study period.

This study raises the possibility that problems with the insulin injection technique are one reason for poor glycemic control. The most common problems observed were repeatedly injecting into the same place, which resulted in stiffness, and pulling the needle out too quickly. Through repeated instruction in correct insulin injection methods, improvement in glycemic control was observed.

CONCLUSION

In conclusion, we have highlighted the importance of re-education in insulin self-injection techniques. Learning insulin self-injection techniques is a great burden for many patients [25]. Efforts should be made to understand patients' personalities and lifestyles and provide patient instruction that explains each step of the technique, as well as the reason for each step, one by one. The ability to increase the patient's self-management capability as a result of this re-education would be a welcome development. We believe that it will also be important to move forward as a team by communicating with other medical staff members, such as nurses

and pharmacists.

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Dr. Yuki Nakatani is the guarantor for this article, and takes responsibility for the integrity of the work as a whole. Medical writing assistance was provided by Angela Morben of Edanz[®] and was funded by Dr. Yuki Nakatani.

CONFLICT OF INTEREST

Yuki Nakatani, Mihoko Matsumura, Tsuyoshi Monden, Yoshimasa Aso, and Takaaki Nakamoto declare that they have no conflicts of interest. No funding or sponsorship was received for this study or publication of this article.

COMPLIANCE WITH ETHICAL GUIDELINES

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients for being included in the study.

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Table 1 Patients' clinical characteristics

Average age	59.3±1.7 years
Male/female ratio	43/44 (<i>N</i> = 87)
Health status: type 1 or 2 diabetes	11/76
Average length of diabetes	15.8±1.0 years
Average length of insulin use	6.6±0.6 years
Average number of injections	2.75±0.10 years
Number of daily injections	Number
1	5
2	38
3	20
4	19
5	4

Data are presented as *n* or mean ± standard error.

Figure 1 The Questionnaire Used in this Study

Q1: Do you lightly tap the syringe or pen barrel with your finger to expel the air?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q2: Do you inject a small amount of insulin?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q3: Do you inject in your abdomen?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q4: Do you rotate injection site?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q5: Do you inject while pinching the skin firmly?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q6: Do you inject perpendicularly to the skin surface?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q7: Do you inject yourself by gently pushing in?
<input type="checkbox"/> Yes <input type="checkbox"/> No
Q8: After how many seconds do you pull the needle out?
<input type="checkbox"/> 0 to 5 seconds <input type="checkbox"/> 6 to 14 seconds <input type="checkbox"/> 15 or more seconds
Q9: Do you hold the injection button down while removing the needle?
<input type="checkbox"/> Yes <input type="checkbox"/> No

Answers were scored with 1 point assigned to a “Yes” answer and 0 points assigned to a “No” answer. However, for Question 8, 0 points were assigned to 0 to 5 seconds, 1 point to 6 to 14 seconds, and 2 points to 15 or more seconds.

Figure 2 The Instructions Given to Patients in this Study

1. There are air bubbles inside the insulin cartridge. Keep the need tip vertical, tap lightly 3 to 4 times.
2. Always do a trial injection. Set the units to 2 and push the inject button firmly to confirm that the insulin comes out. If the insulin does not come out, repeat the trial injection with the units set at 2. However, a new insulin cartridge will require about 6 units of trial injections.
3. We normally recommend an injection into the abdomen. Injections into the abdomen are less painful and are absorbed the quickest, and the insulin is said to change the least after absorption. The abdomen is also said to be least affected by exercise and outside temperature.
4. Injecting into the same location every time may result in the skin becoming inflated or depressed. Please change the location of the injection slightly every time.
5. Insulin is in principle a subcutaneous injection, not an intramuscular injection. Needles used today are short at 5-6mm, and there are some opinions that even if they are injected without pinching the skin, they are unlikely to become intramuscular injections. However, if the injection is made on a skinny person, it may become an intramuscular injection, and if the injection is not made straight, it may become an intradermal injection, leading to worsened glycemic control. Please try to pinch the skin when injecting as much as possible.
6. Whether the angle of injection is 45 or 90 degrees, a firm, deep injection is most effective for insulin absorption.
7. If the insulin needle is pulled out too quickly, liquid may leak out, resulting in worsened control. Please inject by gently pushing in.
8. Please pull the needle out after slowly counting for 15 seconds. If you pull the needle out quickly, insulin may leak out.
9. Please pull the needle out while keeping your finger pushed down on the button. If you let go with your finger, blood may flow back into the injector.

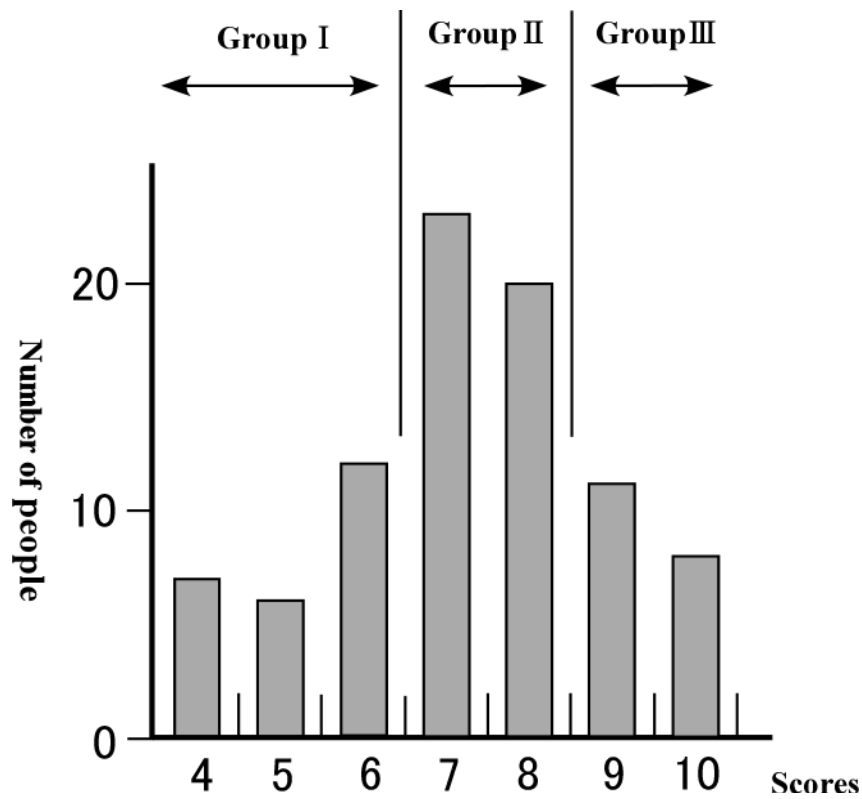


Figure 3 Patient Groups According to Point Score. We divided the patients into three groups (I, II, III) according to point scores. The 25 patients with 4 to 6 points were classified as Group I (poor understanding), the 43 patients with 7 or 8 points were classified as Group II (moderate understanding), and the 19 patients with 9 or 10 points were classified as Group III (good understanding).

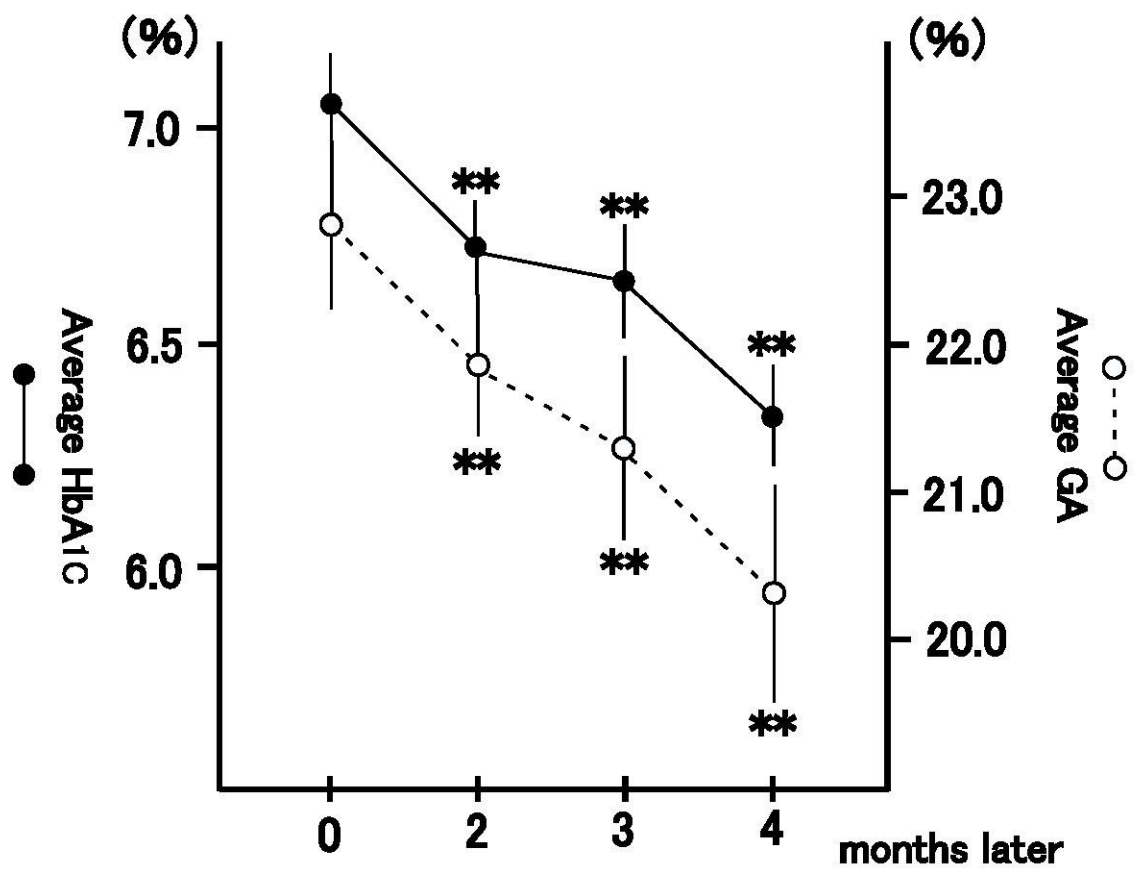


Figure 4 Rate of Decrease of Mean HbA_{1c} and Glycoalbumin Levels. The results shown are given as the mean \pm standard error. **Significant difference between the rate before and after re-education ($P < 0.01$). GA: glycoalbumin; HbA_{1c}: hemoglobin A_{1c}.

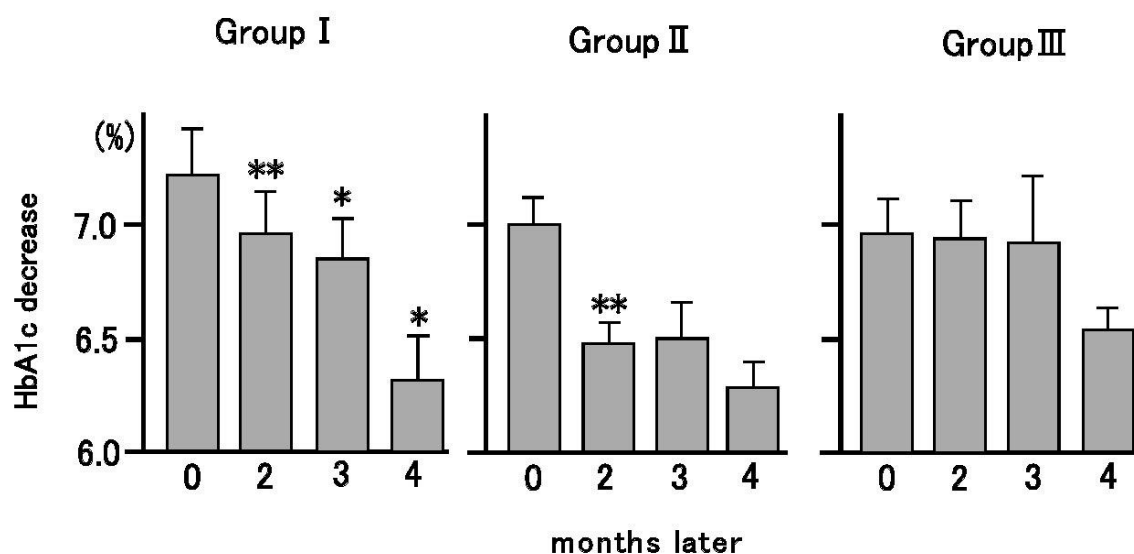


Figure 5 Rate of Decrease of HbA1c Levels. The results shown are given as mean \pm standard error. Group I (poor understanding) showed a significant decrease in HbA1c levels by re-education in all periods (The P value were: 2 months later ($P < 0.01$), 3 months later ($P < 0.05$), and 4 months later ($P < 0.05$)). Group II (moderate understanding) showed a significant decrease 2 months later. (The P value were: 2 months later ($P < 0.01$), 3 months later ($P < 0.06$), and 4 months later ($P = 0.07$)). Group III (good understanding) did not show a significant decrease. (The P value were 2 months later ($P = 0.63$), 3 months later ($P = 0.81$), and 4 months later ($P = 0.09$)). *Significant difference between the rate before and after re-education ($P < 0.05$). **Significant difference between the rate before and after re-education ($P < 0.01$).

Q1: Do you lightly tap the syringe or pen barrel with your finger to expel the air?

☐ Yes

☐ No

Q2: Do you inject a small amount of insulin?

☐ Yes

☐ No

Q3: Do you inject in your abdomen?

☐ Yes

☐ No

Q4: Do you rotate injection site?

☐ Yes

☐ No

Q5: Do you inject while pinching the skin firmly?

☐ Yes

☐ No

Q6: Do you inject perpendicularly to the skin surface?

☐ Yes

☐ No

Q7: Do you inject yourself by gently pushing in?

☐ Yes

☐ No

Q8: After how many seconds do you pull the needle out?

☐ 0 to 5 seconds

☐ 6 to 14 seconds

☐ 15 or more seconds

Q9: Do you hold the injection button down while removing the needle?

☐ Yes

☐ No

1. There are air bubbles inside the insulin cartridge. Keep the need tip vertical, tap lightly 3 to 4 times.
2. Always do a trial injection. Set the units to 2 and push the inject button firmly to confirm that the insulin comes out. If the insulin does not come out, repeat the trial injection with the units set at 2. However, a new insulin cartridge will require about 6 units of trial injections.
3. We normally recommend an injection into the abdomen. Injections into the abdomen are less painful and are absorbed the quickest, and the insulin is said to change the least after absorption. The abdomen is also said to be least affected by exercise and outside temperature.
4. Injecting into the same location every time may result in the skin becoming inflated or depressed. Please change the location of the injection slightly every time.
5. Insulin is in principle a subcutaneous injection, not an intramuscular injection. Needles used today are short at 5-6mm, and there are some opinions that even if they are injected without pinching the skin, they are unlikely to become intramuscular injections. However, if the injection is made on a skinny person, it may become an intramuscular injection, and if the injection is not made straight, it may become an intradermal injection, leading to worsened glycemic control. Please try to pinch the skin when injecting as much as possible.
6. Whether the angle of injection is 45 or 90 degrees, a firm, deep injection is most effective for insulin absorption.
7. If the insulin needle is pulled out too quickly, liquid may leak out, resulting in worsened control. Please inject by gently pushing in.
8. Please pull the needle out after slowly counting for 15 seconds. If you pull the needle out quickly, insulin may leak out.
9. Please pull the needle out while keeping your finger pushed down on the button. If you let go with your finger, blood may flow back into the injector.

Figure
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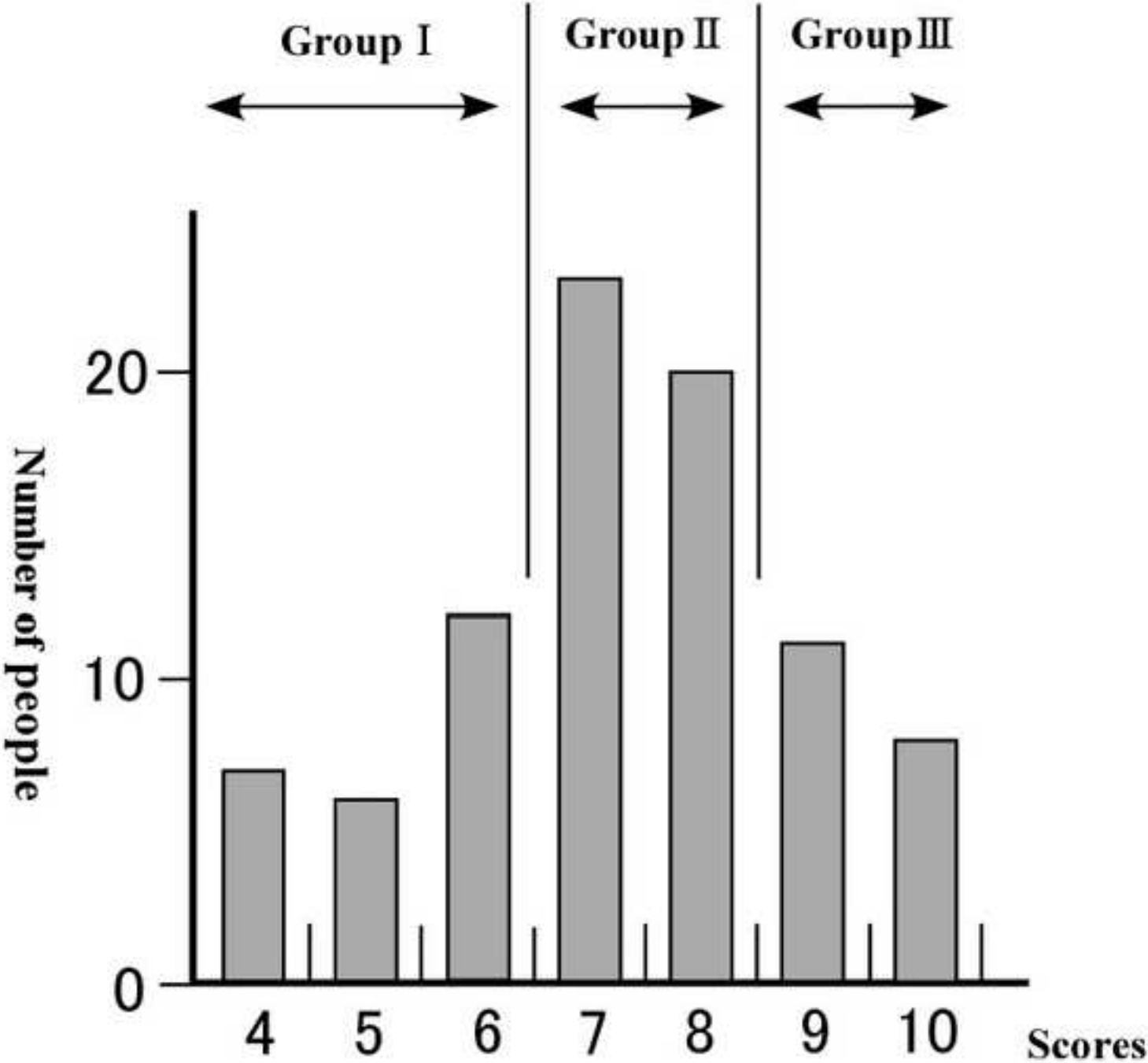


Figure
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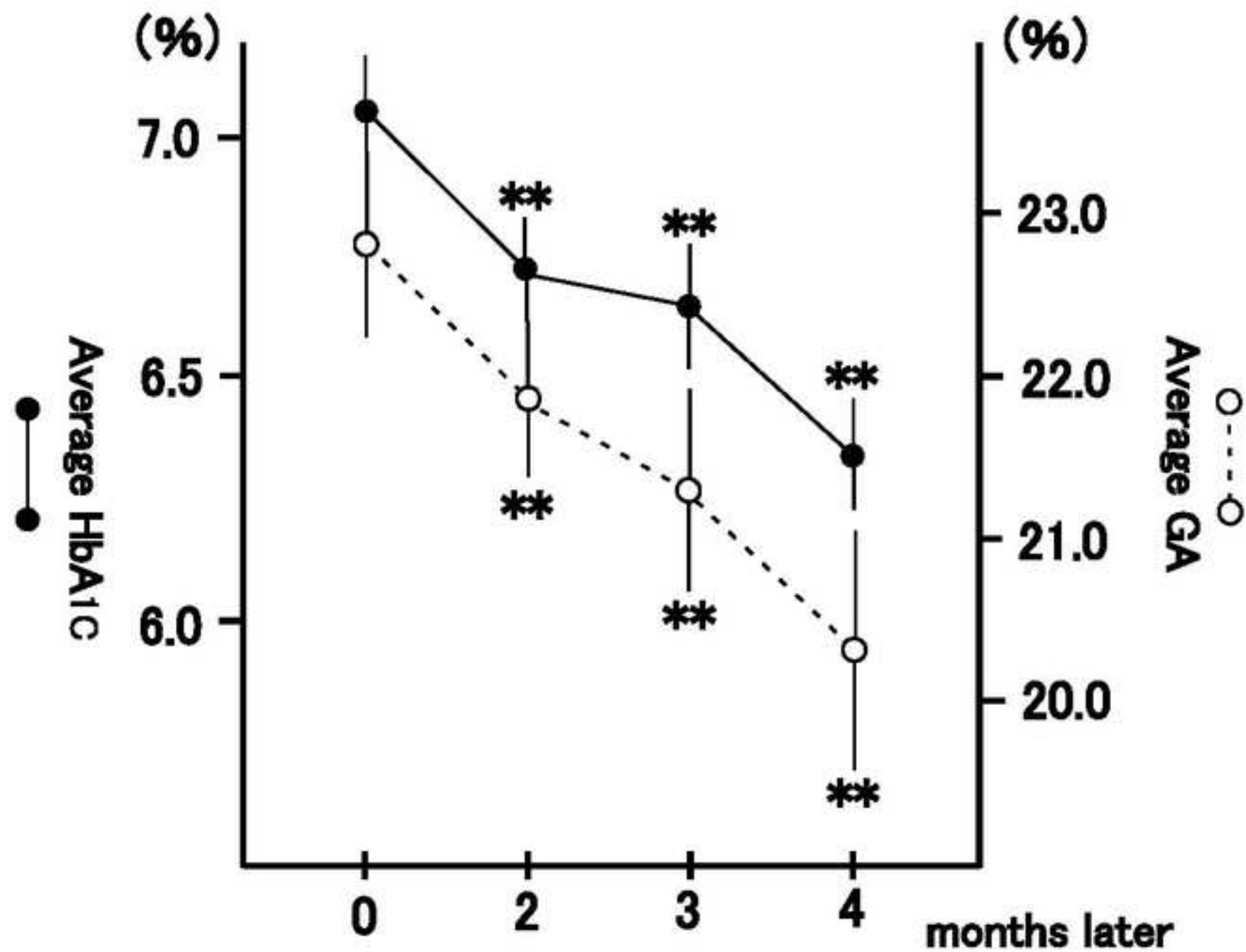
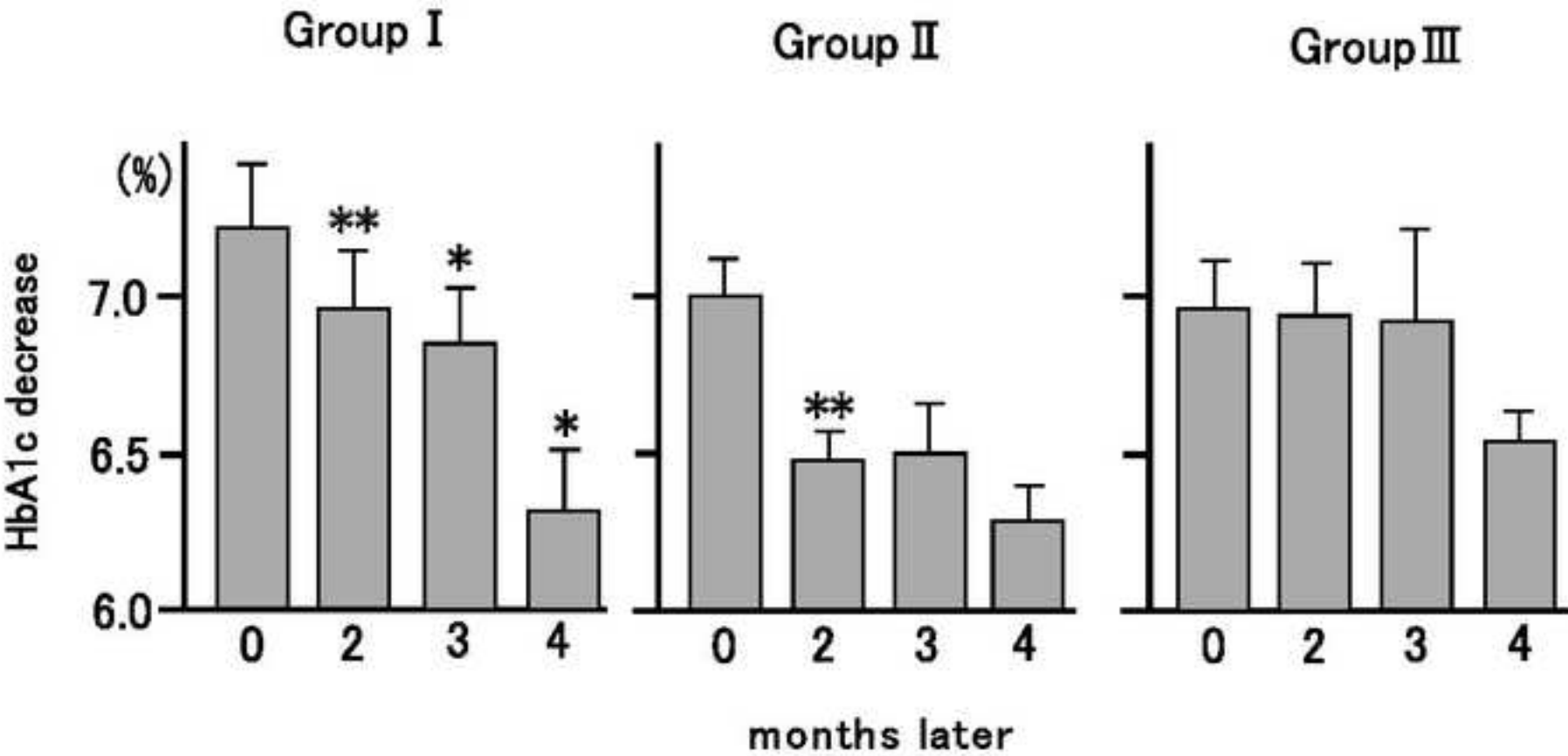


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Key summary points

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