

# Combined Training in the Treatment of Type 2 Diabetes Mellitus: A Review

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## Abstract

This study aimed to review combined training (CT) effects on HbA1c levels in patients with T2DM. Searches were conducted in PubMed via MEDLINE and Google Scholar. Of the 14 selected studies, 11 found reductions in HbA1c levels. The interventions that performed both aerobic and resistance training in the same sessions were highlighted. In aerobic training, the best results were in the interventions between 30 and 45 minutes per session, with intensities between 60 and 80% of maximal parameters. In resistance training, the interventions with sets from 8 to 12 repetitions with intensities of 80% and 60% of 1RM respectively, or prescribed by maximal repetitions, were highlighted. We conclude that CT can result in better glycaemic control than AT and RT conducted alone.

## Keywords

Diabetes, Combined Training, Glycaemic Control, HbA1c

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## 1. Introduction

The growth of non-communicable chronic diseases of endocrine and metabolic character has been raising great concern worldwide, and, in this context, diabetes mellitus (DM) is one of the most common diseases in almost all countries [1]. The new estimates of diabetes in the world population confirm the large burden of the disease, given that the number of diabetic people in 2015 was 422 million, and until 2030 this number is expected to exceed 640 million [2].

Type 2 diabetes mellitus (T2DM), the most common form of the disease (90% - 95% of the cases), results from a combination of insulin resistance with inadequate compensation of this hormone's secretion [3]. Regarding the disease treatment, the three main tools for T2DM management are exercise, diet and

medication [4]. In relation to structured exercise, many studies were conducted and significant reductions were found in the glycaemic responses of individuals who suffer from this disease [5] [6] [7].

The glycaemic control improvement can be evidenced through the levels of glycated hemoglobin (HbA1c) [3], a measurement used for the monitoring of therapeutic interventions efficacy. Stratton *et al.* [8] explain that any reduction in HbA1c levels implies in a lower risk of complications associated to the disease. In this context, systematic reviews regarding physical exercise in T2DM patients showed that structured physical exercise is able to decrease the absolute levels of HbA1c in the blood in about 0.6% [5] [9] [10].

Studies have been conducted searching for optimal training models which can control T2DM, preventing or at least delaying the chronic complications associated to the inadequate control of the disease. In the last decades, the different modalities and forms of manipulation of physical training have been investigated, in which beneficial effects were found with aerobic and resistance training separately performed or combined—aerobic plus resistance—[5]. However, in the meta-analysis of Schwingshackl *et al.* [11], a greater efficacy was found with combined training (CT) in comparison to resistance (RT) and aerobic training (AT) performed alone.

Evidencing its efficacy, there is a need to expand the discussion about manners to optimize combined training structuring for glycaemic control for T2DM patients, discussing characteristics as intervention period, weekly frequency, duration, intensity and order of the modalities. Therefore, the present study aimed to review combined training interventions and its respective effects on HbA1c levels in T2DM patients.

## 2. Methods

Searches were conducted in the databases MEDLINE via PubMed and Google Scholar and the following key words were used: “diabetes”, “exercise”, “combined”, “combined training”, “aerobic”, “resistance”, “HbA1c”, “exercício”, “combinado”, “aeróbico”, “força”, brought together by means of the boolean operator “OR” and “AND”. References lists of review studies were also examined to find other possible eligible studies for the present review. We included studies that performed structured combined training with T2DM patients older than 18 years old, which evaluated changes in HbA1c levels as an outcome (by means or differences between means) at baseline and after interventions, written in English and Portuguese, published between 2000 and 2015. Exclusion criteria were studies of patients with type 1 diabetes mellitus or gestational diabetes, studies that did not report information regarding the associations of the intervention with HbA1c levels in the experimental group or sub-studies of the included interventions.

## 3. Results

Fourteen articles [12]-[25] met the inclusion criteria. Among the eligible studies,

most of them had a control group, except four of them [15] [20] [22] [23]. The main characteristics of the studies are presented in details in **Table 1**.

Of the 14 studies, most of them [12] [13] [14] [16] [17] [18] [19] [21] [23] [24] [25] randomly allocated the subjects. In relation to sex, most of the studies investigated both sexes, except only two studies [13] [15] which investigated post-menopausal women.

## 4. Discussion

The beneficial effects of structured physical training have been well documented in the last decades, presenting improvements in T2DM control, with the improvement in the glycaemic control and reduction of disease-related comorbidities [26]. For the present review, the chosen outcome of glycaemic control was HbA1c levels, which represent the mean glucose concentration in the 8-12 weeks preceding the accomplishment of clinical exams [27]. Analyzing the results of the 14 included studies, 11 found positive responses in the glycaemic control, by significant decreases in HbA1c levels [14]-[20] [22] [23] [24] [25], whereas only three studies did not find improvements in this outcome [12] [13] [21].

It is important to highlight the importance of exercise protocols structuring, because the study of Umpierre *et al.* [5] demonstrated that structured physical training can reduce HbA1c levels more expressively than only the counseling of physical exercise practice. In addition, Oliveira *et al.* [7] claim that combined training structuring is more efficient than the isolated modalities (aerobic or resistance), because the improvement mechanisms of glycaemic metabolism are different and synergistic. Faced with the mechanistic considerations and the clinical evidences, CT has been highly recommended for the glycaemic control of T2DM patients, in which the results have been reported and discussed regarding the intervention characteristics.

### 4.1. Intervention Period

Regarding intervention period, there were studies with short periods (eight weeks) [22], as well as longer ones, with 52 weeks [14] [18] [19] [20]. Associating intervention period to the results found, a superiority of the long-term trainings is not perceived in comparison to the short-term ones, because similar reductions in HbA1c levels were shown after interventions with short periods (0.5% - eight weeks) [22] and medium terms (0.5% to 0.8% - 12 to 20 weeks) [15] [17], with high variability in the results with long term interventions (0.27% to 1.21% - from 20 weeks) [14] [16] [18] [19] [20] [23] [24] [25].

Although the field of T2DM and physical training does not provide studies comparing progressive combined training versus non-progressive combined training, we believe that studies with long term interventions may not expressively impact on glycaemic control because progressions were not conducted in the volume and intensity throughout the interventions. In this sense, it is important to highlight that two [13] [21] of the three studies [12] [13] [21] without

**Table 1.** Responses in combined training in T2DM patients.

Study	Sample (n)	Period	Volume/Intensity	Results in HbA1c levels
Tessier <i>et al.</i> (2000) [12]	Both sexes (CT: 19, CG: 20)	16 weeks	3x/week in circuit AT: 20 min w/intensity progressing from 35% - 59% HR <sub>max</sub> to 60% - 79% HR <sub>max</sub> RT: 2 sets of 20 rep (m.m.g.)	Without significant alterations
Cuff <i>et al.</i> (2003) [13]	Post-menopausal women (CT:10, CG:9)	16 weeks	3x/week Total duration of 75 min per session AT: 60% to 75% HR <sub>res</sub> RT: 2 sets of 12 rep (5 exercises m.m.g.)	Without significant alterations
Balducci <i>et al.</i> (2004) [14]	Both sexes (CT: 51, CG: 53)	52 weeks	3x/week AT: 30 min at 40% - 80% HR <sub>res</sub> RT: 3 sets of 12 rep at 40% - 60% 1RM (6 exercises m.m.g.)	Significant alteration: ↓ 1.21% in comparison to pre-training
Tokmakidis <i>et al.</i> (2004) [15]	Post-menopausal women (CT: 9)	16 weeks	AT: 2x/week (Mondays and Thursdays) 40 - 45 min at 60% - 70% HR <sub>max</sub> progressing to 70% - 80% HR <sub>max</sub> throughout the intervention RT: 2x/week (Tuesdays and Fridays) 3 sets of 12 repetitions at 60% 1RM (5 exercises m.m.g.)	Significant alteration: ↓ 0.80% in comparison to pre-training
Sigal <i>et al.</i> (2007) [16]	Both sexes (CT: 64, CG: 63)	22 weeks	3x/week AT: duration of the sessions progressed from 25 to 45 min and intensity progressed from 70 to 75% of HR <sub>max</sub> RT: 2 to 3 sets of 7 to 9 RM (7 exercises —not-specified)	Significant alteration: ↓ 0.90% in comparison to pre-training ↓ 0.46% in comparison to AT ↓ 0.59% in comparison to RT
Lambers <i>et al.</i> (2008) [17]	Both sexes (CT: 17, CG: 11)	12 weeks	3x/week, in circuit: Walk or light run (10 min), elbow flexion and extension, (10 min), cycling (10 min), knee flexion and extension (10 min), stepping (10 min). AT: progressed from 60 to 85% of HR <sub>res</sub> RT: progressed from 3 series of 10 - 15 rep from 60 to 85% 1RM	Significant alteration: ↓ 0.5% in comparison to pre-training
Church <i>et al.</i> (2010) [18]	Both sexes (CT: 62, CG: 41)	39 weeks	AT: 3x/week. Weekly dose of 10 kcal/kg body mass, among 50 and 80% VO <sub>max</sub> RT: 2x/week 1 set of 10 to 12 RM (9 exercises m.m.g.)	Significant alteration: ↓ 0.27% in comparison to pre-training ↓ 0.38% in comparison to CG
Balducci <i>et al.</i> (2010) [19]	Both sexes (CT: 22, CG: 20)	52 weeks	2x/week AT: 40 min at 70% - 80% VO <sub>2max</sub> RT: 80% 1RM (5 exercises m.m.g.) Training volume increasing in 0.1 kcal/kg body mass/month	Significant alteration: ↓ 1.09% in comparison to pre-training and ↓ 0.94 in comparison to CG
Fatone <i>et al.</i> (2010) [20]	Both sexes (CT: 8)	52 weeks	2x/week AT: 55% - 70% VO <sub>2max</sub> RT: in circuit, progressing from 2 sets of 15 rep at 60% 1RM, to 3 sets of 8 rep at 80% 1RM (4 exercises m.m.g.)	Significant alteration: ↓ 0.45% in comparison to pre-training
Jorge <i>et al.</i> (2011) [21]	Both sexes (CT: 12, CG: 12)	12 weeks	3x/week Total duration of 60 min per session AT: exercise in the cycle ergometer at HR <sub>LT</sub> RT: 7 exercises in circuit m.m.g.	Without significant alterations

## Continued

Touvra <i>et al.</i> (2011) [22]	Both sexes (CT: 10)	8 weeks	4x/week AT: 30 min at 70% - 80% HR <sub>max</sub> RT: 3 sets of 15 rep at 60% 1RM (6 exercises m.m.g.)	Significant alterations: ↓ 0.50% in comparison to pre-training
Larose <i>et al.</i> (2012) [23]	Both sexes (CT: 64, CG: 64)	22 weeks	3x/week AT: progressing from 25 to 45 min at 70% - 75% HR <sub>max</sub> RT: 3 sets of 8 to 12 RM (2 groups of 7 exercises m.m.g.)	Significant alteration: ↓ 1% in comparison to pre-training
Kadoglou <i>et al.</i> (2013) [24]	Both sexes (CT: 22, CG: 24)	26 weeks	4x /week (1 session of AT, 1 session of RT and 2 sessions of AT and RT combined) Total duration of 60 min per session AT: ±30 min at 60% - 75% HR <sub>max</sub> RT: 1 to 2 sets of 8 to 10 repetitions at 60% - 80% 1RM (8 exercises m.m.g.)	Significant alteration: ↓ 0.90% in comparison to pre-training
Stegen <i>et al.</i> (2015) [25]	Both sexes (CT: 59, CG: 61)	26 weeks	3x/week AT: progressing from 15 to 20 min at 60% HR <sub>max</sub> to 45 min at 75% HR <sub>max</sub> RT: 2 to 3 sets of 7 to 9 RM (2 groups of 7 exercises alternatedly performed, m.m.g.)	Significant alteration: ↓ 0.95% in comparison to pre-training

AT: aerobic training, RT: resistance training, CT: combined training group, CG: control group, n: number of participants, RM: maximum repetitions, 1RM: one maximum repetition test, rep: repetitions, ↓ : reduction, HR<sub>max</sub>: maximum heart rate, HR<sub>res</sub>: reserve heart rate, HR<sub>LT</sub>: heart rate at lactate threshold, HbA1c: glycated hemoglobin, VO<sub>2peak</sub>: peak oxygen consumption, VO<sub>2max</sub>: maximal oxygen consumption. %HbA1c: reduction in percentage, m.m.g.: main muscle groups.

significant alterations in HbA1c levels did not perform progression of the trainings, whereas Tessier *et al.* [12] carried out a slight increase in the intensity of the aerobic component. As these studies performed medium-term interventions periods of 12 [21] and 16 [12] [13] weeks, we speculate that the lack of training progression seems to be a failure in training prescription, violating the scientific principle of training overload. Also, in order to combine both aerobic and resistance stimuli in the same session, some studies avoid performing long training sessions, and therefore have a limited time available to perform both components (*i.e.* 20 min, 2 sets). Therefore, it seems that with 12 [21] and 16 [12] [13] weeks of follow-up, the training dosage of these interventions seemed to be low to elicit HbA1c adaptations. It is also important to highlight that another possible explanation for the absence of alterations in the study of Cuff *et al.* [13], is that the participants had low baseline levels of HbA1c, which limited their amplitude of improvement in this outcome.

#### 4.2. Weekly Frequency

The importance of training frequency has been well documented, especially in aerobic training studies. In this direction, a meta-regression analysis conducted by Umpierre *et al.* [6], evaluating the association between physical training intensity and volume and the changes in HbA1c levels in T2DM patients found that weekly frequency is the main determining factor in the glycaemic control by means of aerobic training for this population. Moreover, it is recommended that aerobic training is performed in at least three days of the week, with no more

than two consecutive days between training sessions, due to the short duration nature of the improvements in insulin action [3] [4]. On the other hand, for combined training, the association between weekly frequency and glycaemic control is still not elucidated.

Regarding weekly frequency of the selected studies, two of them performed CT with aerobic and resistance trainings performed in the same days, twice a week [19] [20]; eight studies performed resistance and aerobic trainings in the same days, three times per week [12] [13] [14] [16] [17] [21] [23] [25]; one study performed both trainings in the same days, four times per week [22]; one study performed resistance and aerobic trainings in alternated days, being twice a week for each one [15]; one study performed one weekly session of aerobic training, one weekly session of resistance training and two weekly sessions combining both training types in the same session [24]; and one study conducted aerobic training in three weekly sessions and resistance training twice a week [18].

According to ADA [3], physical exercise recommendations for T2DM patients are at least three weekly sessions of aerobic training and two weekly sessions of resistance training. All the interventions performed the minimum recommendation for resistance training. Eleven of the interventions [12] [13] [14] [16] [17] [18] [21] [22] [23] [24] [25] are in accordance with the minimum weekly frequency for aerobic training. Of these, only three studies did not find reductions in HbA1c levels [12] [13] [21]. On the other hand, although the other studies did not reach the minimum weekly frequency recommended for aerobic training [15] [19] [20], all of them found reductions in HbA1c levels. These reductions could have resulted from other interventions characteristics performed, as the three studies performed progressions in volume and/or intensity throughout the interventions, which, according to Fleck and Kraemer [28], can optimize the results, that is, these interventions may have generated new physiological stimuli across the interventions, consequently resulting HbA1c reductions.

Additionally, it is important to highlight that the studies which found the most expressive reductions in HbA1c levels (decreases of 0.95% to 1.21%, **Table 1**) were those conducting both aerobic and resistance trainings in the same days, in three and four weekly sessions [14] [19] [23] [25]. All these studies had progression of the training variables. Moreover, in two of these interventions [23] [25] a significant volume of exercises were performed for the resistance training component (14 exercises each, with 3 sets of 8 - 12 sets of 7 - 9 maximum repetitions, respectively), which is in accordance with the results found in the meta-regression of Umpierre *et al.* [6], attributing the weekly volume of resistance training exercises to the HbA1c reductions resulting from CT.

### 4.3. Duration and Intensity

Over the years, well designed studies have been attributing the success of physical training interventions not only to the modality but also to some training va-

riables. In a meta-analysis conducted by Boulé *et al.* [9], physical training intensity was associated to reductions in HbA1c levels in a greater extent than training volume. Later, Umpierre *et al.* [5] demonstrated that weekly duration was fundamental for HbA1c reductions, independently of the training modality. On the other hand, Umpierre *et al.* [6] showed that in aerobic training the only training variable associated to glycaemic reduction was weekly frequency, whereas any strength training variable was associated to glycaemic reduction and, in CT, only the number of sets in the resistance component presented this association.

Regarding the management of AT duration and intensity for T2DM patients, it is recommended that it must be performed for at least 150 minutes per week with moderate to high intensity, disseminated into three weekly sessions, with no more than two consecutive days between training sessions [4]. Of the 14 studies selected, four did not report session durations [13] [18] [20] [21] and only three studies did not find reductions in HbA1c levels [12] [13] [21]. Thus, we verified that the reality of these studies which reported the training durations does not contemplate ADA [3] guidelines for aerobic training duration. These findings corroborate the meta-regression analysis of Umpierre *et al.* [6], which did not evidence association between AT duration and HbA1c levels reduction resulting from CT, being the RT number of sets the variable associated to glycaemic control through this training modality. Faced with that, it becomes necessary a further reflection about training guidelines for T2DM people, as other training characteristics (and not the training duration of 150 minutes) may be attributed to reductions in HbA1c levels of this population.

We believe that finding positive results with weekly durations shorter than 150 minutes in AT can positively impact on training adherence, which is fundamental for the success of physical training interventions. With the advancement of modern and busy life, with often long working hours, in which people have increasingly less free time to exercise, it is important that physical training is time-efficient to help individuals to reach their goals and keep maintaining an active and healthy life.

In the present review, the studies adopted different intensity markers. In AT, seven studies prescribed training intensity using percentages of maximum heart rate ( $HR_{max}$ ) [12] [15] [16] [22] [23] [24] [25], three used percentages of heart rate reserve ( $HR_{res}$ ) [13] [14] [17], three used percentages of maximum oxygen consumption ( $VO_{2max}$ ) [18] [19] [20] and one study conducted it through the heart rate corresponding to lactate threshold ( $HR_{LT}$ ) [21]. Of the selected studies, those that used the intensities prescribed between 60 and 75% of  $HR_{max}$  (15 to 45 min/session) [25], 70% to 75% of  $HR_{max}$  (25 to 45 min/session) [23], 70% to 80% of  $VO_{2max}$  (40 min/session) [19], and the intensities between 40% and 80% of  $HR_{res}$  (30 min/session) [14] for AT were those that found the greater reductions in HbA1c levels.

It is important to highlight that, among the articles included in the present re-



view, 10 of them [12] [15] [16] [18] [19] [20] [22] [23] [24] [25] used percentages of  $HR_{max}$  and  $VO_{2max}$  for AT prescription. It is well known that the exercise performed in a certain percentage of  $VO_{2max}$  or  $HR_{max}$  can induce different physiologic responses for different individuals, and that submaximal parameters as anaerobic threshold are better indicators for aerobic training prescription [29]. Moreover, the anaerobic threshold determination method through heart rate deflexion point, which has low cost, easy application and was associated to the second ventilatory threshold in T2DM patients [30], was not used in any of the reviewed studies. Therefore, we emphasize that there are other possibilities with greater metabolic precision, which have not been used in studies with T2DM patients.

In relation to the management of RT intensity, seven studies performed it by means of percentages of one repetition maximum (1RM) test [14] [15] [17] [19] [20] [22] [24], two used 7 to 9 maximum repetitions [16] [25], one adopted 10 to 12 maximum repetitions [18], one used 8 to 12 maximum repetitions [23] and three studies did not specify the way that RT intensity was conducted [12] [13] [21]. Most of the studies maintained the intensity fixed throughout all the interventions periods, whereas five studies progressed RT intensities at some point of the intervention [12] [15] [17] [20] [23]. Of these, only one [12] did not find significant alterations in HbA1c levels. Regarding the best results found [14] [19] [23] [25], the intensities between 7 to 9 maximum repetitions, 8 to 12 maximum repetitions, 80% of 1RM and from 40% to 60% of 1RM were respectively used.

#### 4.4. Number of Exercises in RT

The selected studies for the present review adopted different numbers of exercise for the resistance training component of the CTs. The number varied from two exercises (one for upper and one for lower limbs) [17], six exercises for the big muscle groups [14] [22] to fourteen exercises [23] [24] [25], also for large muscle groups.

Although the ADA indications are of 8 to 12 resistance exercises prioritizing the big muscle groups [3] [4], an analysis of this parameter in the reviewed studies demonstrates that this is not a determining factor for glycaemic control, because studies with similar number of exercises induced different responses. It becomes clear by analyzing the number of RT exercises in the four studies with the best results in HbA1c, because whereas Stegen *et al.* [25] and Larose *et al.* [23] performed 14 exercises in their interventions, Balducci *et al.* [14] performed six exercises and Balducci *et al.* [19] performed five exercises. Thus, we believe that other training variables, as intensity, number of sets and repetitions may have greater relevance in the combined training programs structuring, as well as training variables progression, aiming to periodically induce new physiological adaptations in T2DM individuals, and consequently the glycaemic control for this population.



#### 4.5. Order of the Modalities

In the reviewed studies, different manners of performing the order of resistance and aerobic trainings were applied. Of these, six studies [13] [14] [16] [19] [22] [25] performed AT before RT in the same training sessions; three studies [12] [17] [21] conducted both training modalities in the same session, in circuit; one study [15] performed AT and RT in separate days; one study [24] used one weekly session for AT, one weekly session for RT and two weekly sessions with both training types, without specifying the order; one study [23] allowed the participants to choose the training order; whereas the other studies [18] [20] did not report the training order. Of the four studies that showed the best results in the glycaemic control, three of them performed AT before RT in the same sessions [14] [19] [25] and one of them allowed the participants to choose the order [23].

CT has been widely explored in the literature, and in this context, the interference effect has also emerged, which explains that the expected results from RT suffer interference of AT, that is, the strength development is impaired when AT precedes RT [31], whereas cardiorespiratory fitness does not suffer the same impairment when it is performed after RT [32]. The order effect has not yet been investigated in T2DM population, therefore, there is a doubt whether the training order could interfere in the interventions results, if some order could maximize glucose uptake and possibly result in a better glycaemic control. In addition, we also emphasize that the training order could be investigated regarding training adherence, which is a very important issue to be considered in the clinical population. Besides the training order be pre-established by physical exercise professionals, there is also the possibility of the patient to choose the order, which could also positively influence on adherence to interventions.

#### 4.6. Comparisons between CT with AT and/or RT

In the present review, three studies compared CT with AT [13] [17] [19], one study compared CT with RT [23], and five studies compared CT with both aerobic and resistance trainings separately performed [16] [18] [21] [24] [25]. Of these, only one study did not find significant results in HbA1c levels in both aerobic and resistance trainings [13].

In the intervention conducted by Lambers *et al.* [17], comparing AT and CT groups, only CT found HbA1c reductions, whereas the other studies [16] [18] [19] [21] [24] [25] found greater reductions in HbA1c levels with CT in comparison to other groups that performed AT or RT alone. These results show that every time that CT was compared with AT or RT isolated, CT induced greater results. Other important issue is that in the study of Church *et al.* [18] performed with three intervention groups (AT, RT and CT) only CT group participants underwent reduction in HbA1c values. Although this decrease was not very expressive, this reduction was significant, showing that in a long training period (52 weeks), in which there was not progression of the training variables, it seems

that only the combination of aerobic and resistance stimuli was able to sustain the gains reached in the first months of training.

## 5. Conclusions

Faced with the studies selected for the present review, we can conclude that combining aerobic and resistance trainings can induce a better glycaemic control than these interventions performed alone. However, the great number of different methods adopted in the several studies limits our ability to provide the optimal exercise strategy for T2DM management.

Despite this, faced with the characteristics of the included studies, we can state that the interventions that induced the greater reductions in HbA1c levels had the weekly frequency from three to four times a week (with AT and RT performed in the same days). Regarding aerobic training intensity and duration, the best results were shown with the interventions that used training prescription with durations between 30 and 45 minutes per session, with intensities among 60% and 80% of maximal parameters. In the resistance component, the results with sets of 8 to 12 repetitions in the intensities of 80% and 60% of 1RM, respectively, or in the same number or repetitions prescribed by maximum repetitions, with exercises for the big muscle groups, were highlighted. We emphasize that sedentary patients can initiate training programs in volume intensities below the indicated ones, and continuously increase it throughout the interventions, by means of progression of the training variables.

We believe that future studies should investigate CT specific characteristics, as its performance in alternate days (AT and RT) versus in the same session, as well as the order of accomplishment of aerobic and resistance modalities.

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