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The 6-minute walk-test in type 2 diabetics predicts to some extent maximal aerobic capacity but not its training-induced improvement

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Keywords: Type 2 diabetes mellitus; 6-minute walk test; Ventilatory threshold; Cardiorespiratory fitness; VO₂max; Training

Abstract

Objective: Six-minutes' walk-test (6MWT) is a measure of physical fitness widely studied and validated in chronic pathologies with sedentary lifestyles. It is an aerobic fitness test, correlated with maximum oxygen consumption (VO_{2max}) in some studies, but this correlation is not well established in diabetes. We assessed the extent to which it predicts VO₂max and its training-induced changes in type 2 diabetics.

Materials and methods: Twenty-five type 2 diabetics were randomized and divided into two groups: 13 completed a physical training program (eight hospital education sessions continued at home through two weekly 30-45-minute sessions at an intensity corresponding to the first ventilatory threshold VT₁) and the remaining 12 continued their usual treatment unchanged.

Results: After 1 year training maintained maximum aerobic capacity, while it decreased significantly in the untrained group (p=0.014). Voorrips' activity score was correlated with VO_{2max} (r= 0.44, p= 0.05) and with the distance walked at 6MWT (r=0.446, p=0.05). The distance walked during 6MWT is correlated with VO_{2max} before (r= 0.456 p= 0.05) and after (r= 0.714 p<0.001) and on all values measured before and after (r= 0.571 p= 0.01). The change in MWT does not predict that of VO₂max to which it is not correlated (r=0.318; NS), but it is weakly correlated to that of the VT₁ (r= 0.435 p=0.05) while the absolute values of VT₁ and 6MWT are not correlated at all. 6MWT was not correlated with HbA_{1c}.

Conclusions: as in other sedentary populations, 6MWT is an indicator (approximate but easy and economical) of aerobic fitness. However, it does not measure training-induced changes in aerobic fitness, its variations being rather a marker of those of the first ventilatory threshold.

Introduction

The six-minute walk test (6MWT) is a simple and costless measure of physical fitness which was proposed in the 80's [1]. It has later been shown to be correlated with maximum oxygen consumption (VO_{2max}) in healthy individuals [2,3] and also to reflect the ability to oxidize lipids at exercise [4]. Since it has been widely studied and validated in chronic

pathologies associated to sedentary lifestyles [5-8], it appears to be logically more and more employed in diabetes studies [9]. However, the basis for this use was until recently poorly documented. Recently three papers evidenced relationships between 6MWT and maximal oxygen uptake (VO_{2max}) in specific groups of diabetic patients [10-12]. All of them concluded that 6MWT is correlated to VO_{2max} and concluded that it can be employed as a marker of aerobic capacity. However, these

encouraging reports are still preliminary. They rely on quite limited samples of subjects: 54 South-Korean T2D women aged 50–70 years [10], 18 north American T2Ds included in the randomized controlled trial ACTIVE II [11] and 42 Spanish T2M with a mean age of 61.1 years [12]. Whether conclusions of these studies in selected populations can be safely extended to other populations remains to be more investigated. In addition, whether the evolution of 6MWT after training reflect a change in VO_{2max} remains unknown, and this is a fundamental question to address before counselling the wide use of 6MWT as a reliable surrogate of aerobic working capacity measurements.

VO_{2max} is an important physiological parameter [13], since it is the most recognized index of cardiorespiratory fitness, whose impairment is associated with many adverse health outcomes. By contrast the measurement of VO_{2max} requires a maximal exercise-test which cannot be performed everywhere and requires a specific and expensive material. Therefore, reliable surrogates providing an evaluation of cardiorespiratory fitness are useful for a comprehensive assessment of an individual's health, and 6MWT is surely one of the most attractive because it is simple to realize and costless [1,5–8]. If it were also a good reflect of health improvement after treatment its interest would be even greater but this remains unknown for diabetics, since in this disease there are several factors of disability (eg, neuropathy, retinopathy). That are not directly linked with cardiorespiratory fitness.

The database of a previous study of training in diabetics [14] in order to investigate the cost-reducing effect of exercise in T2D provides us an opportunity to answer to those two important questions:

- Is the previously reported correlation between 6MWT and VO_{2max} confirmed in this separate sample, supporting the idea that this relationship should be expected to exist in the general population of T2D?
- Is a change in MWT after training a reliable predictor of an improvement un working aerobic capacity in these patients?

Materials and methods

Study participants

This study is part of a wider study investigating the effects of exercise training individually targeted at the level of VT_1 on healthcare costs for chronic diseases, that included 112 patients: 45 with chronic obstructive pulmonary disease (COPD), 32 with chronic heart failure, and the 25 with type 2 diabetes. The sample of 25 type 2 diabetics is presented on Table 1. More data can be found in the paper presenting all the results and investigating the main endpoint of the trial [14].

Patients routinely followed by their general practitioner were recruited into the study. Diabetes was defined according to the to the 1997 criteria of the American Diabetes Association [14]. Patients were eligible for the study if they were aged 40–85 years and if they fulfilled the following criteria:

- Treatment with oral hypoglycaemic agents or diet alone, and not with insulin therapy;
- HbA1c level between 8 and 10%;
- No change in any medication for the past three months;
- No history of ketoacidosis.

Patients with congestive heart failure, a recent episode of ischemic heart disease, peripheral vascular disease, current malignancy, chronic renal failure, severe proliferative diabetic retinopathy or any physical and mental conditions that may have an influence on the ability of the patient to participate in the intervention were excluded. The study protocol was approved by the institutional review board of the University Hospital of Montpellier. All patients gave their informed consent to participate in the study.

Body composition

The patients were measured, weighed on a Sartorius F1505-F2 balance scale and had their waist circumference measured at the umbilicus. Body composition was assessed with a four-terminal impedance plethysmograph (Dietosystem

Table 1: Anthropometric, ergometric and metabolic parameters measured in the untrained versus trained diabetic patients at the beginning and end of the study.

	Untrained		Trained		Intra- and intergroup comparisons
	Day 0	Day 365	Day 0	Day 365	
Gender ratio F/M	5/7		4/9		ns
Duration of diabetes (years)	10.3 ± 1.7		10.3 ± 1.7		ns
Age (years)	60.6 ± 1.8		58.9 ± 3.6		ns
Height (cm)	167.56 ± 12.16		168.17 ± 8.13		ns
HbA1c (%)	8.83 ± 1.38	8.56 ± 1.5	8.77 ± 0.98	8.46 ± 1.66	ns
VO ₂ max (mL/min/kg)	15.5 ± 1.2	12.7 ± 2.0	20.8 ± 1.2*	19.0 ± 2.0**	*P = 0.005 vs. untrained, Day 0** P = 0.008 vs. untrained, Day 365
VT (% theoretical VO ₂ max)	49.35 ± 11.7	49.87 ± 14.2	50.04 ± 13.2	51.6 ± 12.5	VT (% theoretical VO ₂ max)
Maximum power	99.8 ± 47.7	69.7 ± 33.5*	113.3 ± 34.9	118 ± 45.6	*P = 0.018 vs. Day 0
Difference in maximum power reached		-22.6 ± 30.06		7.23 ± 40.1*	*P = 0.041
Walking distance (m)	461 ± 26	458 ± 23	555 ± 18	559 ± 17*	*P = 0.002 vs. untrained, Day 365

Human IM-Scan, Milan, Italy), which minimizes contact impedance and skin-electrode interactions. Measurements were taken in fasting patients after 15 minutes of rest in a supine position. A low-intensity (100–800 μ A) current was introduced at various frequencies (1, 5, 10, 50 and 100 kHz), and measurement of the voltage drop allowed determination of the total body impedance rate. These values are then used with specially designed software to calculate body water (intra- and extracellular), fat mass, fat-free mass and body cell mass [16].

Exercise testing

The patient's VO_{2max} was measured during 8–12 minutes of exercise performed on an electronically braked cycloergometer (550 ERG, Bosch, Germany). During exercise, gas exchanges were measured breath by breath, using a mass spectrometer (Marquette MGA 1100, France). The calibration of the mass spectrometer was checked before each test with standard calibration gases. A 3-L syringe was used to calibrate the volume turbine, using flow rates similar to the patient's ventilation. Heart rate was monitored throughout the exercise test, which started with a six-minute warm-up at 20% of the theoretical maximum power output. The workload was then increased by steps of 8% of Pmax per minute until the maximum exercise level was reached, which was then evaluated in terms of maximum heart rate, Respiratory Exchange Ratio (RER) (>1.15) and O_2 consumption (VO_2) stability. The results of this test were used to determine the first ventilatory threshold (VT_1) according to the method used by Beaver, et al. [17], and [18]. The maximum theoretical oxygen consumption ($VO_{2max\ th}$) and, thus, the theoretical Pmax were also calculated, according to Wasserman's equations [19]. Criteria for defining VO_{2max} and VT_1 were taken from the standardization consensus guidelines of the French Society of Sports and Exercise Medicine [18,20].

The six-minute walking shuttle test (6 MWT) was conducted as described by Guyatt, et al. [1,21]. Using a corridor in the outpatients clinic, a 15-meter course was marked out, placing a chair at each end. The decision whether the patient was fit enough to take the 6 MWT was made by the attending cardiologist. Patients were instructed to walk at their own pace from end to end while attempting to cover as much ground as possible in the allotted six-minute time period. A physiotherapist clocked the walking and called out the time every two minutes, while also encouraging the patient on. Patients were allowed to rest, but were instructed to carry on walking as soon as they were able to do so. After six minutes, patients were instructed to stop walking, and their total distance was measured to the nearest meter. Any symptoms experienced by the patient during this test were also recorded. Blood pressure was measured before and after the test.

Physical activity level was assessed using the Voorrips questionnaire [22].

Training intervention

This was a parallel-group, randomized trial. On Day 1, patients were randomly assigned to one of two groups using a computer-generated list of random numbers. In the

intervention group, patients were told to follow the training programme while, in the control group, the intervention consisted of repeated evaluation of fitness, healthcare cost assessment and metabolic parameters. Patients in both groups continued to be managed by their own primary-care physician, and there was no study interference with the physicians' therapeutic choices. The only modification from the study was the addition of structured exercise training in the intervention group. All treatments, health events and hospitalizations were recorded by the investigators at each visit for calculation of the healthcare costs.

The structured training programme comprised of an educational period of one month, followed by training at home. The educational period involved eight two-hour sessions over four weeks, when a trained professional, during the first hour, explained to the patient the purpose of the training and how it should be performed. The second hour was devoted to actually learning the exercise that the patient had to perform - in this case, cycling at the level of the ventilatory threshold for 30–45 minutes at a time. After this learning session, the patient had to train at home twice a week at a level defined by heart rate. All participants performed, at their own convenience, brisk walking, jogging or gymnastics for 45 minutes at this target heart rate, as determined by a heart-rate monitor.

To ensure "realistic" conditions of training, the actual practice of the physical activity was recorded: everyday, patients had to keep track of all their activity in a notebook, and fill in Voorrips questionnaires on Days 120, 240 and 365.

Both study groups were followed over the course of the year by evaluations at 30, 120, 240 and 365 days to determine healthcare costs, blood pressure, spirometry, glycaemic and lipid equilibrium, 6 MWT, and exercise [16] and QOL questionnaires. A further maximum-level exercise test to determine VO_{2max} and ventilatory threshold was performed at Day 0 and Day 365 as described above.

Statistical analyses

Data are shown as means \pm S.E.M. Statistical analysis was performed with Sigmapstat (<https://systatsoftware.com/products/sigmatat/>) and the Bland-Altman and Altman plot was done with the freeware "method validator" Philippe Marquis (<https://method-validator.software.informer.com/>). Correlation analyses were performed on EXCEL.

Results

On entering the study, the participants appeared to have similar values of HbA1c (8.8% \pm 1.38 versus 8.77 \pm 0.98%), fasting blood glucose, weight, height, BMI, waist circumference and blood pressure. As previously reported [13], after 1 year of targeted training protocol, trained subjects maintained their maximum aerobic capacity, while this capacity significantly decreased in the untrained group ($p=0.014$). Distance walked during the 6 MWT did not decrease in the trained group and became significantly higher in this group than in the untrained group at the end of the period of training. Voorrips' activity

score was correlated with VO_{2max} ($r=0.44$, $p=0.05$), as well as with the distance walked during the 6MWT ($r=0.446$, $p<0.05$).

As shown on Figure 1, walking distance measured during the 6MWT is correlated with VO_{2max} before ($r=0.456$ $p<0.05$). This correlation is also found after training as shown on Figure 2 ($r=0.714$ $p<0.001$). When pooling values obtained before and after training there is also a highly significant correlation ($r=0.571$ $p<0.01$) as shown on Figure 3. From the latter correlation analysis we can propose a prediction of VO_{2max} with the equation:

$$VO_{2max} = 0.034 [6MWT] + 0.6653$$

where VO_{2max} is expressed in ml/min/kg and 6MWT in meters. On Figure 4, we show the Bland-Altman plot evaluating the agreement between actual VO_{2max} and VO_{2max} predicted by the abovementioned equation. It can be seen that differences between predicted and actual VO_{2max} are well centered around the central line but that the range of differences is rather high (-12 to +12 ml/min/kg).

Since an equation predicting VO_{2max} from 6MWT and weight

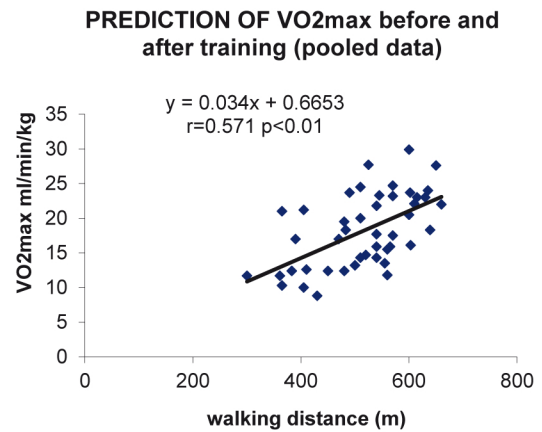


Figure 3: 6MWT-derived walking distance in the patients of the study before and after 1 year of individualized training (pooled data).

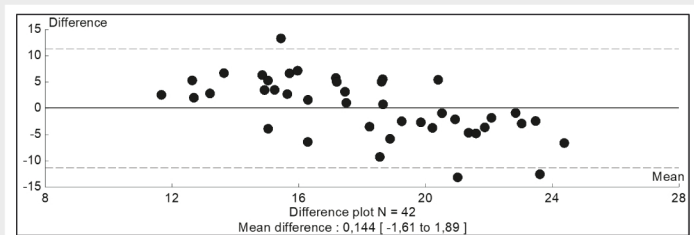


Figure 4: Bland-Altman plot evaluating the agreement between actual VO_{2max} and VO_{2max} predicted by the equation given by Fig. 3: $VO_{2max} = 0.034 [6MWT] + 0.6653$.

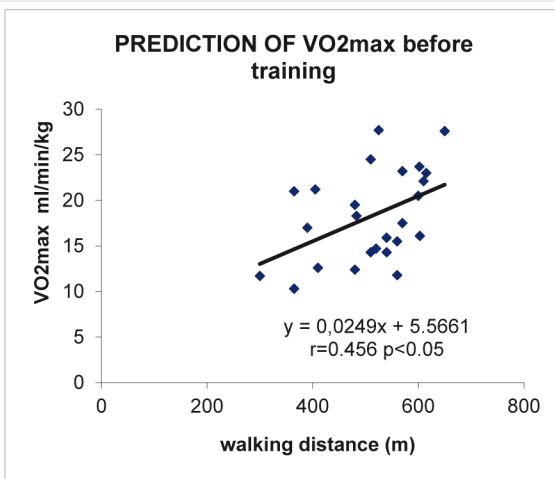


Figure 1: 6MWT-derived walking distance in the patients of the study in baseline conditions before the onset of the training program.

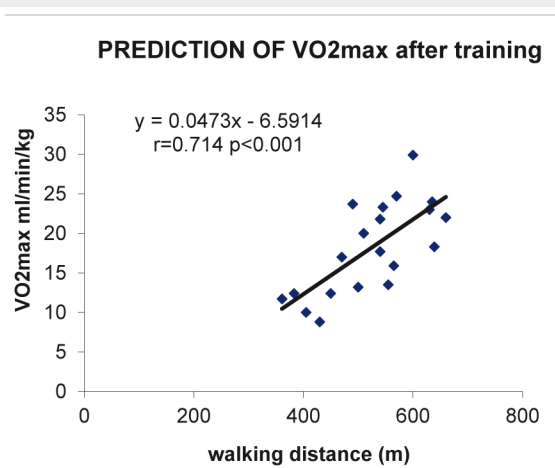


Figure 2: 6MWT-derived walking distance in the patients of the study after 1 year of individualized training.

was proposed in Lee's paper [10], we tested this equation in our sample. The equation is:

$$VO_{2max} = 14.986 + 0.025 [6MWT] - 0.161 \text{ weight.}$$

Actually these correlations did not reach significance. Before training we found $r=0.274$ (NS), after training we found $r=0.339$ (NS) and for values before and after pooled together we found $r=0.299$ (NS). Therefore this equation proposed in a South Korean population doesn't work in our sample.

We also looked for correlations between changes in 6MWT and changes in VO_{2max} and VT_1 . As shown on Figures 5,6, changes in 6MWT-derived walking distance in the patients of the study before and after 1 year of individualized training (pooled data) are not linearly correlated with changes in VO_{2max} ($r=0.317$ NS) but if a nonlinear model is applied a highly significant polynomial relationship is evidenced, showing that the change in MWT may predict the decrease in VO_{2max} but not an improvement in VO_{2max} .

By contrast changes in MWT after 1 year are not correlated with those of VO_{2max} despite a loose tendency ($r=0.318$; NS). These changes are by contrast weakly correlated to that of the SV_1 ($r=0.435$ $p<0.05$) while the crude values of SV_1 and 6MWT are not correlated.

We also looked for correlations between 6MWT and HbA1c since such correlations were reported in previous papers. We found no correlation at all with r values as low as $r=0.0216$ before training; $r=0.099$ after training and $r=0.037$ for values before and after pooled together.

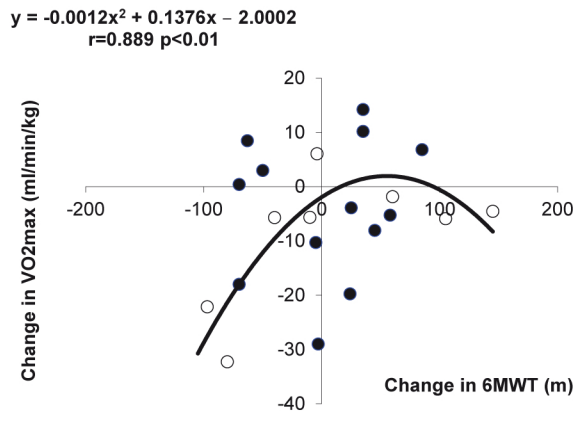


Figure 5: 6MWT-derived walking distance in the patients of the study before and after 1 year of individualized training (pooled data). White circles: trained subjects; black circles: untrained subjects.

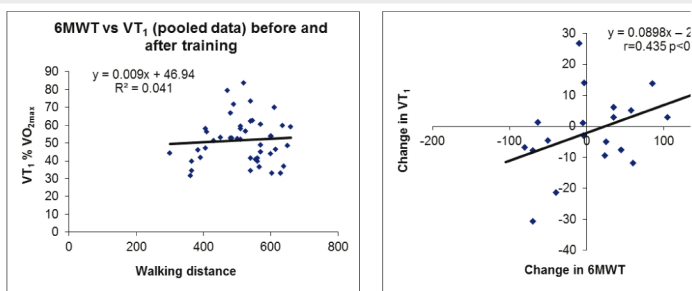


Figure 6: Relationships between 6MWT-derived walking distance in the patients of the study and ventilatory threshold (VT₁) before and after 1 year of individualized training (pooled data). Left panel: complete lack of correlation between 6MWT and VT₁. Right panel: low significance correlation between changes in 6MWT and changes in VT₁.

Discussion

This study shows that, as already reported other sedentary populations [5–8] and in healthy individuals [2–3], 6MWT is an index, approximative but easy to obtain and inexpensive, of aerobic working capacity. Actually, we also show that post-training changes in 6MWT are unable to reflect the training-induced changes in $VO_{2\max}$ and rather reflect changes in ventilatory threshold.

These findings are useful for investigators using more and more the 6MWT test in diabetic patients, because there is a tendency to consider that this test is an accurate monitoring of aerobic capacity and some recent papers could lead to think so [10–12]. Actually we demonstrate that this is not fully exact and that although the walking distance provided by the test is correlated to $VO_{2\max}$, changes in those two parameters after training are poorly related. An improvement in walking distance in diabetics does not closely reflect an improvement in $VO_{2\max}$.

This study is part of a wider study investigating the effects of exercise training at the level of VT₁ and one of the findings was that $VO_{2\max}$ declined by 16.4%, over 1 year without training while this decline was prevented by training. Although it is well accepted that diabetes is a progressive disease [23], such a rapid decline highlights the “vicious circle” of a sedentary

lifestyle in chronic diseases [24], and characterized by rapid deterioration even at the stage of disease where patients are comparatively healthy. In this regard, it is noteworthy that our “realistic” lifestyle intervention, albeit not particularly aggressive, was nonetheless able to prevent such a decline.

This important finding of a preventing effect on training on the decline in $VO_{2\max}$ in T2D is not clearly found with our 6MWT data, but a close look at the data suggests that this may become significant on a larger sample.

Nevertheless, as shown on Figure 4, 6MWT seems to be sensitive to a decrease in $VO_{2\max}$ and thus may be helpful for detecting an impairment in aerobic capacity in this population. By contrast it is not sensitive to an increase in $VO_{2\max}$ and cannot detect it.

In fact, it is not surprising to find some discrepancies between 6MWT and $VO_{2\max}$ data, which by essence are not the same measurement and cannot provide exactly the same information. Correlations between $VO_{2\max}$ and 6MWT found in the 3 previous studies [10–12] yield quite the same values of coefficients of correlation, ranging between 0.456 and 0.66. Nolen-Doerr [11] analyses this fact as reflecting that 6MWT distance alone ‘explains’ 45% of the variance of $VO_{2\max}$, so that 55% of this variance is not ‘explained’ by it.

Interestingly, Nolen-Doerr [11], reports a higher coefficient of correlation after training ($r=0.66$) compared to pre-training ($r=0.57$), and this is fully consistent with the current study which shows $r=0.456$ before training and $r=0.714$ after training. This may reflect an improvement in cardiovascular regulatory adaptation to exercise strengthening the agreement between the two measurements.

In contrast to other studies we were unable to evidence a correlation between diabetic control as measured by HbA_{1c} and the 6MWT. There was absolutely no correlation between these two parameters. Such a correlation was reported by Ramírez Meléndez [12] and is logic to expect since poor glucose control drives the complications of diabetes which in turn induce disability. However, in samples of patients like those of the study, who are followed regularly, this correlation can be hidden by recent improvements in blood glucose control.

Both $VO_{2\max}$ and 6MWT are indexes of fitness whose interest in chronic disease is obvious, because they integrate a host of factors and represent an overall evaluation of health. This was impressively demonstrated some years ago by the correlation between $VO_{2\max}$ and insulin sensitivity [25]. Therefore, measuring a parameter of fitness that integrates cardiovascular, respiratory and metabolic health is surely important in diabetics, although this is not yet systematic. In this respect measuring 6MWT offers the advantage of easiness and low cost, and it is clear that this measurement provides an important information.

Attempts to derive from crude 6MWT data an accurate prediction of $VO_{2\max}$ provide quite deceiving results, and it is probably better to consider that those two parameters have not exactly the same meaning and should not be considered as equivalent.

This study has strengths and limitations. One of the strengths is to present precise measurements of VO_{2max} obtained during a maximal exercise test before and after a period of training and with an untrained control group. The randomized design of the study is also a strength. We think that the duration of one year of the study is more relevant to real life healthcare than a shorter period as often found in training studies. Clearly, training needs to be applied for long periods in patients, and short-term training studies in chronic diseases barely reflect this reality. Another strength of the study is that it was designed to represent the average population of type 2 diabetics of our country, although it is clear that T2DM occurs more and more earlier in western countries. By contrast, a limitation of the study is that it was designed for assessing training-induced changes in healthcare costs and not for comparing 6MWT and VO_{2max} . Therefore, the number of subjects was not calculated before the study for this purpose. This may induce a risk of type-2 error, as discussed above concerning the lack of training effect on 6MWT which contrast with the training-induced prevention of a decline in VO_{2max} which is clearly evidenced. It is likely that a greater number of subjects would allow us to evidence a training effect on 6MWT. Nevertheless, it is clear than the two parameters do not evolve in close parallelism and that they have not exactly the same meaning.

More precisely, we can say that our study fully confirms the precedent report of some degree of correlation between 6MWT and VO_{2max} but also points out the discrepancy between these two parameters which have not exactly the same relevance. 6MWT can provide an estimate of an individual's fitness in chronic diseases, and it is clear that this is an interesting and useful marker of health. By contrast, changes in 6MWT may reflect other improvements than those of aerobic working capacity and are not a tool do precisely detect such improvements in diabetes.

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