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ORIGINAL ARTICLE

6-Min walk-test data in healthy North-African subjects aged 16–40 years

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KEYWORDS

6-Min walk-distance;
Norms;
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Abstract *Background:* In North-African and Mediterranean countries (such as Algeria, Tunisia, Morocco, Libya) no local 6-Min walk-distance (6MWD) norms exist for subjects aged 16–40 years.

Aims: (i) To test the applicability and reliability of the previously published norms for Arab or Mediterranean subjects aged $\geqslant$ 16 years in this population and, if required, (ii) to establish a 6MWD reference equation for use in North-African subjects aged 16–40 years and prospectively assess its reliability and to propose a clear scheme to interpret the measured 6MWD.

Study design: Prospective cross-sectional study.

Methods: Metabolic-equivalent-task (MET) walking, moderate, and vigorous activities, anthropometric, spirometric and 6-Min walk-test (6MWD, heart-rate, oxy-haemoglobin-saturation) data were measured/noted in 200 healthy Algerian subjects aged 16–40 years (100 women). Univariate and multiple linear regression analyses were used to find-out 6MWD influencing factors, reference equation and to determine the lower-limit-of-normal (LLN).

Abbreviations: ATS, American-Thoracic-Society; BMI, body-mass-index; COPD, chronic-obstructive-pulmonary-disease; DBP, diastolic-blood-pressure; ERS, European-Respiratory-Society; FEV_1, first-second-expiratory-volume; FFM, fat-free-mass; FVC, forced-vital-capacity; Hr, heart-rate; IPAQ, international-physical-activity-questionnaire; LAOVD, large-airways-ventilatory-obstructive-defect; LLN, lower-limit-of-normal; MET, metabolic-equivalent-task; mHr, predicted-maximal-heart-rate; MMEF, maximal-mid-expiratory-flow; Oxy-sat, oxy-haemoglobin-saturation; r, correlation-coefficient; r^2, determination-coefficient; RSD, residual-standard-deviation; SBP, systolic-blood-pressure; SD, standard-deviation; TRVD, tendency-to-a-restrictive-ventilatory-defect; ΔHr, $Hr_{end-rest}$; 6MWD, 6-min walk-distance; 6MWT, 6-min walk-test; 95%CI, 95% confidence-interval; end, at the end of the 6MWT; rest, before the 6MWT

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Results: The mean ± SD of 200 included subjects' age, height, weight, body-mass-index (BMI), lean-mass, first-second-forced-expiratory-volume (FEV_1) and MET moderate activity were, respectively, 27.5 ± 6.7 years, 169 ± 9 cm, 69.3 ± 11.5 kg, 24.1 ± 3.6 kg/m^2, 16.7 ± 7.4 kg, 3.70 ± 0.74 L and 370 ± 686 min/week. Their 6MWD mean ± SD (minimum–maximum) was 680 ± 70 (540–888) m. The published norms for Italian and Saudi-Arabian populations did not reliably predict measured 6MWD. The following 6MWD influencing factors were noted: FEV_1, BMI, sex, lean-mass, MET moderate activity and age ($p < 0.001$). A reference equation, explaining 58.7% of the 6MWD variability, was established: 6MWD (m) = 800.05 + 64.71 × Sex (men:1/women:0) − 10.23 × BMI (kg/m^2) − 1.63 × Age (years) + 2.05 × Weight (kg). To calculate the 6MWD LLN subtract 74.31 m from the predicted value. In a second group of 39 young subjects (19 women) prospectively studied to validate the reference equation, the agreement between the measured and predicted 6MWDs was adequate.

Conclusion: This reliable 6MWD norm is helpful for the care of North-African patients aged 16–40 years.

Introduction

Exercise testing is increasingly utilized in clinical practice to optimize patient management and acquire useful functional and predictive information not accessible through static cardiopulmonary tests, such as spirometry and/or electrocardiogram [1–5]. Among the available variety of exercise testing protocols for this purpose; the 6-Min walk-test (6MWT) is an inexpensive and expeditious test of functional ability [1–4]. It is a self-based walking test that measures the distance walked over a 6-Min period (6MWD) [1,3]. It is frequently used to evaluate exercise capacity in patients with chronic diseases [2–4,6–8]. The interpretation of this test, which is more wistful of daily living activities than other walk tests [1–3], relies on the comparison of measured 6MWD with the normal predicted value from reference equations or norms [1,2,9–36].

Normal predicted values for 6MWD are often based on sex and anthropometric data (eg, age, height and weight) [1,4] and the influence of race and/or ethnicity is still ambiguous [1,18]. At the best of the authors knowledge, only three 6MWD norms were published for healthy Arab "adults" populations [9–11]; two for Tunisians older than 40 years [9,10] and one for Saudi aged 16–50 years [11]. In addition, among all published studies aiming to establish 6MWD norms in healthy adults [9–36] only one included young Mediterranean ones; Italians aged 20–50 years [12]. In North-African Mediterranean countries (such as Algeria, Tunisia, Morocco, Libya) no local 6MWD norms existed for subjects aged 16–40 years and norms derived from Arab [11] or Mediterranean [12] populations are commonly used. This was the case of two recent studies aiming to evaluate the functional capacity of exclusive-narghile-smokers [7] and obstructive-sleep-apnoea-hypopnea-syndrome patients [8]. This is a problematic practice, since the applicability and trustworthiness of these norms has never been verified in the local population, even though several specificities have been noted concerning ethnic background, anthropometric data, physical activity status, etc. [37]. The use of these 6MWD norms [11,12] may lead to invalid clinical analysis of 6MWT data [4,10,26]. In a multicenter study, the 6MWD norms varied in function of the geographic site; therefore, different countries need specific equations [26]. Moreover, the answer to the question of which 6MWT norm should be used in chronic-obstructive-pulmonary-disease (COPD) patients, was that the choice should be specific for the country/region of origin [38]. Furthermore, the American-Thoracic-Society/European-Respiratory-Society (ATS/ERS) promote investigators to publish norms for healthy persons using the 6MWT guidelines [1,3].

Although physical inactivity may lead to increased risk of long-term disability and co-morbidity [24,39], the relationship between the physical activity status and the 6MWD of healthy subjects is controversial [10,11,14–16,24–26,30,31,33]. In some studies [10,14], it was shown to correlate, albeit poorly, with the 6MWD. Other studies [11,15,16,25,30,31,33] found no significant correlations between the 6MWD and physical activity status evaluated by several ways [40–43]. In addition, in the study [24] applying the international-physical-activity-questionnaire (IPAQ-8) [44], no data were reported about the relationship between measured 6MWD and physical activity levels'.

Yet, lean-mass is a predictor of exercise capacity in healthy subjects [45], and at the best of the authors knowledge, no study aiming to establish norms in healthy subjects aged ⩾ 16 years [9–36] has evaluated its relationship with measured 6MWD. This is a further criticism, because the classical measured anthropometric data may not cover all the important anthropometric information that may be required to explain 6MWD variability'. In COPD, 6MWD was similar in patients with and without lean-mass depletion, indicating that the skeletal muscle has limited influence on 6MWD [46]. Specific studies on the influence of lean-mass on 6MWD of healthy adults are needed,

Making a medical judgment is an art, where test results help to confirm or decline the diagnosis [47]. A test result is regarded as well-matched with disease if it is outer to the normal range [47]. In young subjects, the last can be determined by three methods: tables of reference centile by age-decade [23], calculating the lower-limit-of-normal (LLN) [14,19,20,22,24] or fixing a percentage (81% of predicted value [15]) below which the 6MWD is considered abnormal. In some studies [13,16–18,21], especially the Saudi and the Mediterranean ones [11,12], no interpreting scheme was proposed.

The aims of the present study were as follows:

(i) To determine the factors influencing 6MWD in healthy Algerian adults aged 16–40 years, with particular attention to physical activity status and lean-mass.
(ii) To test the applicability and reliability of the previously published norms for Arab [11] or Mediterranean [12] subjects aged ⩾ 16 years in this population and, if required.
(iii) To establish a 6MWD reference equation for use in North-African subjects aged 16–40 years and prospectively assess its reliability and to propose a clear scheme to interpret the measured 6MWD.

Population and methods

This prospective study was performed over a 18-month period at the clinical Physiology and Functional Exploration Department of BEN BADIS Hospital in the Eastern region of Algeria (Constantine region, 649 m above sea level).

Study design

Subjects aged ⩾ 18 years were recruited among local Hospital and Medical School workers and/or students. Adolescents aged 16–18 years were the offspring of Hospital and Medical School workers. Informational letters clarifying the aims of the study were put up at the Hospital departments and the local Medical School.

The study was conducted in compliance with the 'Ethical principles for medical research involving Human subjects' of Helsinki Declaration (available from: http://www.wma.net/en/30publications/30ethicsmanual/pdf/ethics_manual_arabic.pdf, accessed June 19th; 2015). Approval for the study was obtained from the Hospital ethics committee (approval number 2211/2013). The approval specifically covered the inclusion of subject aged 16–18 years. Written informed consent was obtained from all study participants aged ⩾ 18 years and from the parents of included adolescents.

Data from each volunteer subject included: sex, age, height, weight, body-mass-index (BMI), lean-mass, fat-free-mass (FFM), smoking history, medication use, medical history, physical examination, physical activity questionnaire and spirometry data. The 6MWT was then performed. All subjects received a copy of their tests results and when an unsuspected dysfunction was revealed, they were sent to a specialist.

Sample size

The sample size estimation was based on the following formula [48]: $n = (Z_{\alpha/2})^2\, s^2/d^2$, where "$s$" (= 52 m) is the 6MWD SD' obtained from a Saudi-Arabian study [11] and "d" (= 10 m) is the accuracy of the estimate or how close to true mean. "$Z_{\alpha/2}$" is a normal deviate for two-tailed alternative hypothesis at a level of significance ($Z_{\alpha/2}$ is 2.58 for 1% level of significance). The required number of subjects was estimated to be 180. This estimated number was increased by 10% to account for attrition and missing values. The final estimated number was 200.

To verify the reliability of the present study 6MWD norm, 6MWD was prospectively measured in a second group of 39 additional healthy subjects (19 women) who met the study inclusion-criteria and had not participated in the first part.

Subjects

Healthy volunteer subjects aged 16–40 years [49] were included. Non-inclusion criteria were: age ⩾ 40 years, the usual 6MWT counter-indications [3] [unstable angina or myocardial infarction during the preceding month; resting heart-rate (Hr_{rest})] ⩾ 120 bpm, resting systolic- or diastolic-blood-pressures (SBP_{rest}, DBP_{rest}), respectively ⩾180 mmHg and ⩾100 mmHg], current or ex-smokers, symptoms of- or confirmed cardiopulmonary disease [heart-failure or arrhythmia, major electrocardiogram abnormalities, lower limb arteritis, dyspnoea (modified medical research council scale) ⩾ stage two, chronic cough, COPD, emphysema, asthma, wheezing, interstitial fibrosis, pulmonary tuberculosis, cerebrovascular accident], diabetes, thoracic or abdominal surgery, orthopaedic disease interfering with walking, mental disease, marked and extreme obesity and chronic medication use (corticoids, diuretics, adrenergic β-antagonists). Exclusion-criteria were: incapability to perform exactly the 6MWT, large-airways-ventilatory-obstructive-defect (LAOVD), tendency-to-a-restrictive-ventilatory-defect (TRVD), resting oxy-haemoglobin-saturation (oxy-sat_{rest}) ⩽92%, end 6MWT dyspnoea (visual-analogue-scale) > 5/10 and walking induced desaturation (oxy-sat fall > 5 points).

Medical and physical activity questionnaires

A medical questionnaire recommended for epidemiological investigation was used to assess numerous subject characteristics [50].

Physical activity was evaluated using the IPAQ-8 short version (www.ipaq.ki.se/scoring.pdf, accessed June 19th, 2015) [44]. It includes questions about duration and intensity of physical activity on a "usual" week in occupational, transport, leisure or sport activities. A French version of the IPAQ-8 was filled out by each subject, and metabolic-equivalent-task (MET) walking, moderate, and vigorous activities were evaluated to yield a MET total activity score, (min/week). Three levels (low, moderate and high) of physical activity were identified [44] and two physical activities statuses [active (high physical activity level); non-active (low and moderate physical activity levels)] were arbitrarily identified.

Physical examination

The decimal age was calculated to the nearest 0.01 years from the date of measurement and the date of birth. Height (± 1 cm) was measured with a height gauge (standing stadiometre type DETECTO®) with shoes removed, heels joined, and back straight. Weight (± 1 kg) and FFM (kg) was measured using an impedance metre (TANITA Corporation 1-14-2, Maeno-Cho, Itabashi-ku Tokyo Japan). Lean-mass (weight – FFM) and BMI (weight/height^2) were calculated.

The following definitions were adopted [51]: underweight (BMI < 18.5), normal weight (18.5 ⩽ BMI ⩽ 24.9), overweight (25.0 ⩽ BMI ⩽ 29.9), moderate obesity (30.0 <

BMI < 34.9); marked obesity ($35.0 \leqslant BMI \leqslant 39.9$) and extreme obesity ($BMI \geqslant 40.0$).

Spirometry measurements

Spirometric measurements (ZAN 100, Megreräte GmbH, Germany) were performed [52]. The results [first-second-forced-expiratory-volume (FEV_1), forced-vital-capacity (FVC), FEV_1/FVC and maximal-mid-expiratory-flow (MMEF)] were compared with local spirometric norms [37]. LAOVD was defined as a "FEV_1/FVC ratio < LLN" [53]. A record with "FEV_1 < LLN" and "FVC < LLN" and "FEV_1/FVC > LLN" was considered as a TRVD [54].

6MWT procedure

The 6MWT procedure was widely described in previous studies aiming to establish 6MWD norms for healthy North-African children [55] or adults' ⩾ 40 years [10].

Two 6MWTs were supervised by the same physician (MKB) according to international guidelines [3] 6MWTs were made along a 30 m corridor marked every one metre with cones to indicate turnaround points. To reduce intraday variability, temperature effects and biological rhythms, the 6MWT was done between 8 a.m. and 12 noon, a period characterized by a stable ambient temperature of 15–21 °C. At the end of each minute, subjects were given feedback on the elapsed time and homogeneous encouragement in the form of statements such as "you're doing well," and "do your best." All subjects performed the 6MWT for the first time with no warm-up phase and they were told to avoid forceful exercise in the two hours prior to testing and to wear comfortable clothes and suitable walking shoes [10].

The subjects sat on a chair situated near the starting site for at least ten minutes before the test started. During this time, dyspnoea, Hr and oxy-sat (Medlab Nanox 2) and blood-pressures were measured at rest ($_{rest}$). The test directives to the volunteers were those recommended by the ATS [3]. At the end ($_{end}$) of the 6MWT, the same data, in addition to 6MWD, were measured/noted. Hr was expressed as bpm and as a percentage of predicted maximal-Hr [$mHr = 208 - 0.7 \times Age$]. As recommended [3], the second 6MWT began ~20–45 min after the first one, in order to achieve comparable initial Hr_{rest} [12–14,16,17,19].

Data analysis

The results of the 6MWT having the utmost 6MWD were selected for statistical analysis [13,17,19]. Preliminary descriptive analysis included frequencies for categorical variables. The variables are presented as mean ± SD and 95% confidence-interval (95%CI) if normally distributed or median (1st–3rd quartiles) if skewed.

Univariate and multiple regression analysis (influencing factors)

The dependent variable (6MWD) was normally distributed. *T*-tests were used to evaluate the associations between 6MWD and categorical variables (sex and physical activity status) and Pearson product-moment correlation-coefficient (*r*) evaluated the associations between 6MWD and continuous ones [height, age; weight, BMI, lean-mass, FFM, FEV_1 (L), FVC (L), MMEF (L/s), SBP_{rest}, DBP_{rest}, Hr_{rest} and MET walking, moderate and vigorous activity scores]. The linearity of the relationship between 6MWD and the continuous data was graphically verified by scheming each regressor against 6MWD. Only significantly and linearly associated data were entered into the model. A linear regression model was used to evaluate the independent data explaining the 6MWD variance. Candidate variables were stepped into the model with a stepwise selection method. To determine entrance and elimination from the model, significance levels of 0.15 and 0.05 were used, respectively. No colinearity between predictors was noted with variance inflation factors.

Comparison with commonly used norms in young North-African adults

S1 Table detailed Arabian and Mediterranean studies [11,12] commonly used in North-African subjects aged 16–40 years.

Measured 6MWDs were compared with predicted ones from the commonly used norms [11,12] for the same age range as in the related study, in two ways. Limits-of-agreement were used for comparison, with individual difference between measured and predicted 6MWD plotted against the corresponding mean value [56]. From these data, limits-of-agreement were then calculated (mean difference between measured and predicted 6MWD ± 1.96 SD) [56]. Comparisons also integrated paired *t*-tests between measured and predicted values.

6MWD reference equations

According to guidelines [1,3], interpretation of the 6MWD should preferably be made by considering age, height, weight and sex, variables shown to independently influence healthy subjects 6MWT data [9–17,19–36]. For this reason, norms were established using those data as predictors of 6MWD in other stepwise linear regression models. The latter were evaluated by the determination-coefficient (r^2) and the standard-error.

The residual-SD (RSD = (measured 6MWD − predicted 6MWD)/SD of the predicted 6MWD) and the LLN ($= 1.64 \times RSD$) were calculated. A measured 6MWD lower than the LLN was considered abnormal.

Reliability of the simplified reference equation

As done in some studies [11,13,14], the reliability of the present simplified 6MWD norm was evaluated in an additional group of 39 healthy subjects. The measured 6MWDs were compared with the predicted ones from the simplified 6MWD norm. The latter will be qualified as appropriate for Algerian subjects aged 16–40 years, if no statistical significant difference will be found between predicted and measured 6MWD values and if no subject will have a measured 6MWD value < LLN.

All statistical procedures were performed using statistical software (Statistica Kernel version 6; Stat Software. France). Significance was set at the 0.05 level.

Results

An initial sample of 258 volunteers (120 women) was examined. Non-inclusion and exclusion-criteria were found in 19 subjects [smokers ($n = 12$), BMI > 35 kg/m^2 ($n = 5$), LAOVD and TRVD ($n = 2$)].

Approximately 84% of the studied population ($n = 200$) was randomly selected for inclusion in a predictive equation, while the remaining subjects ($n = 39$) were used as validation group.

Demographic, anthropometric, spirometric and 6MWT data

The anthropometric and spirometric data and MET scores of the included men ($n = 100$) were significantly different from those of the women ($n = 100$), except for age, BMI, FEV_1/FVC, MMEF (%) and MET moderate activity (Table 1). One hundred and eight subjects (48 women), ten (six women) and nine (five women) showed, respectively, normal weight, moderate obesity and underweight. Fourteen adolescents aged 16–18 years were included.

The 6MWT data are shown in Table 2. 6MWTs were well tolerated and none of the 6MWTs were interrupted before the 6-min mark. Wide 6MWD range (540–888 m) was noted for the total sample. The total sample 6MWD is shown in S1 Fig. according to age, height and weight ranges.

Univariate analysis

Sex significantly influenced the 6MWD (Table 2). On average, the 6MWD value was 92 m greater in men when compared to women ($p < 0.05$).

On average, the 6MWD value was 36 m greater in active subjects ($n = 54$) when compared to non-active ones ($n = 146$) ($p < 0.05$).

S2 Table shows the r^2 between the measured 6MWD and subjects' data. The total sample 6MWD was significantly correlated with age, height, FFM, lean-mass, BMI, FVC (L), FEV_1 (L), MMEF (L/s), MET walking, moderate, vigorous and total activity scores, Hr_{rest} and SBP_{rest}.

Multiple regression analysis: Influencing factors

Table 3 presents the cumulative r^2 of the independent influencing factors incorporated in the 6MWD linear multiple regressions. Up to 62% of the total sample 6MWD variability' could be explained by six variables: FEV_1, BMI, sex, lean-mass, MET moderate activity and age.

Comparison with published regression equations

Fig. 1 shows, for the same age range, the comparisons between measured and predicted 6MWD from the Italian (Fig. 1A) and Saudi (Fig. 1B) norms. There was a difference between measured and predicted 6MWD from these two norms, which was always statistically significant. Indeed, mean ± SD measured 6MWD was significantly overestimated by 3 ± 45 m and was significantly underestimated by 210 ± 58 m, respectively, with the Mediterranean [12] and the Saudi [11] norms.

6MWD simplified norm

Due to the inadequacy of the commonly used norms [11,12] in Algerian subjects aged 16–40 years, local adapted 6MWD

Table 1 Characteristics of the included healthy North-African subjects.

		Women ($n = 100$)	Men ($n = 100$)	Total sample ($n = 200$)
Age	(Year)	27.64 ± 6.45	27.39 ± 6.91	27.52 ± 6.67
Height	(cm)	162 ± 5	177 ± 6*	169 ± 9
Weight	(kg)	64.13 ± 9.78	74.45 ± 10.70*	69.29 ± 11.46
Fat-free-mass	(kg)	42.65 ± 3.64	59.89 ± 6.37*	51.03 ± 10.06
Lean-mass	(kg)	20.59 ± 7.02	12.67 ± 5.41*	16.74 ± 7.42
Body-mass-index	(kg/m^2)	24.0 ± 3.8	23.9 ± 3.4	24.1 ± 3.6
FVC	(L)	3.58 ± 0.40	5.05 ± 0.53*	4.32 ± 0.87
FVC	(%pred)	88 ± 8	94 ± 9*	91 ± 9
FEV_1	(L)	3.10 ± 0.36	4.30 ± 0.49*	3.70 ± 0.74
FEV_1	(%pred)	88 ± 8	93 ± 9*	91 ± 9
FEV_1/FVC (absolute value)		0.87 ± 0.05 (0.86 to 0.88)	0.85 ± 0.05 (0.84 to 0.86)	0.87 ± 0.05 (0.85 to 0.87)
MMEF	(L/s)	3.64 ± 0.72	4.63 ± 1.09*	4.12 ± 1.04
MMEF	(%pred)	80 ± 14	76 ± 16	78 ± 15
MET walking activity	m/w	803 ± 810	1679 ± 1952*	1239 ± 1552
MET moderate activity	m/w	446 ± 558	292 ± 79	370 ± 686
MET vigorous activity	m/w	442 ± 669	795 ± 1250*	617 ± 1014
MET total activity	m/w	1691 ± 1221	2767 ± 2373*	2226 ± 1955
Physical activity levels				
Low participation		32 (32.0%)	21 (21.0%)#	53 (26.5%)
Moderate participation		52 (52.0%)	41 (41.0%)	93 (46.5%)
High participation		16 (16.0%)	38 (38.0%)#	54 (27.0%)

Data are mean ± SD except for the physical activity levels where data are number (%).
FEV_1: first-second-forced-expiratory-volume. FVC: forced-vital-capacity. m/w: min/week. MET: metabolic-equivalent-task. MMEF: maximal-mid-expiratory flow. pred: predicted.
* $p < 0.05$ (t-test): men vs. women.
# $p < 0.05$ (chi-2): men vs. women.

Table 2 6-Min walk-test (6MWT) data of the included healthy North-African subjects.

		Women (n = 100)		Men (n = 100)		Total sample (n = 200)	
		Rest	End	Rest	End	Rest	End
Heart-rate	(bpm)	83 ± 10	140 ± 19	78 ± 10*	131 ± 21*	80 ± 10	135 ± 20
Heart-rate	(%pred)	44 ± 5	74 ± 9	41 ± 5*	69 ± 11*	42 ± 5	72 ± 10
Systolic-blood-pressure	(mmHg)	112 ± 11	138 ± 19	119 ± 11*	146 ± 17*	116 ± 11	142 ± 18
6MWD	Measured (m)	634 ± 49		726 ± 55*		680 ± 70	
	Predicted (m)	637 ± 28		729 ± 25		683 ± 53	
	Measured (%pred)	100 ± 6		100 ± 7		100 ± 7	
Oxy-haemoglobin saturation	(%)	98 (96–98)	98 (96–98)	97 (96–98)*	97 (96–98)*	97 (96–98)	97 (96–98)
Diastolic-blood-pressure	(mmHg)	70 (60–75)	60 (50–70)	70 (60–80)*	60 (50–70)	70 (60–80)	60 (50–70)

Data are mean ± SD for heart-rate, systolic-blood-pressure and 6MWD.
Data are median (1st–3rd quartiles) for oxy-haemoglobin saturation and diastolic-blood-pressure.
Heart-rate (%pred): heart-rate expressed as a percentage of the maximal predicted heart-rate. 6MWD: 6-Min walk-distance. 6MWD (%pred): 6MWD expressed as a percentage of the present study retained reference equation.
* $p < 0.05$: men vs. women.

Table 3 Independent variables included in the multiple regression models for the 6-Min walk-distance (6MWD).

Independent variables		B	95% CI around B	Cumulative r^2	P level	SE
Women (n = 100)						
Constant		419.88	182.13 to 657.64		0.01	144.97
Body-mass-index	(kg/m^2)	−3.38	−5.38 to −1.37	0.219	0.02	
FEV_1	(L)	16.48	−7.74 to 40.70	0.304	0.26	
DBP_{rest}	(mmHg)	−0.61	−1.32 to 0.09	0.326	0.15	
Height	(cm)	2.01	0.44 to 3.57	0.345	0.03	
Age	(Year)	−1.42	−2.69 to −0.15	0.368	0.06	
Men (n = 100)						
Constant		813.71	702.44 to 924.98		0.02	67.85
Body-mass-index	(kg/m^2)	−8.22	−11.49 to −4.95	0.191	0.01	
FEV_1	(L)	28.77	12.33 to 45.22	0.281	0.01	
MET moderate activity		0.01	−0.02 to 0.00	0.307	0.04	
Lean-mass	(kg)	2.57	0.24 to 4.91	0.333	0.07	
DBP	(mmHg)	−0.62	−1.46 to 0.21	0.344	0.22	
Total sample (n = 200)						
Constant		698.04	633.91 to 762.18		0.01	39.11
FEV_1	(L)	30.54	−9.03 to −4.59	0.504	0.02	
Body-mass-index	(kg/m^2)	−6.84	17.52 to 43.55	0.569	0.01	
Sex	(men:1/women:0)	59.41	39.25 to 79.57	0.602	0.03	
Lean-mass	(kg)	1.60	0.29 to 2.92	0.610	0.04	
MET moderate activity	(m/w)	0.01	0.00 to 0.02	0.617	0.06	
Age	(Year)	−0.73	−1.66 to 0.19	0.620	0.19	

95% CI: 95% confidence-interval. B: non standardized regression coefficient. DBP: diastolic-blood-pressure. FEV_1: first-second-forced-expiratory-volume. m/w: min/week. MET: metabolic-equivalent-task. P: probability. r^2: determination-coefficient. SE: standard-error.
Proposed model for the total sample: 6MWD (m) = 698.04 – 6.84 × body-mass-index + 30.54 × FEV_1 + 59.41 × Sex + 1.60 × Lean-mass + 0.01 × MET moderate activity – 0.73 × Age.

reference equation was established (Table 4). For useful, daily reading of 6MWD values, and as norms should incorporate only simply measured anthropometric data [1,3], three simplified 6MWD norms with five common parameters (sex, BMI, age, weight and height) were established for women, men and total sample. The total sample single model [6MWD (m) = 800.05 + 64.71 × Sex (men:1/women:0) – 10.23 × BMI (kg/m^2) – 1.63 × Age (Year) + 2.05 × Weight (kg)] appeared to clarify 59% of the 6MWD variability. Therefore, it was retained as the norm for Algerian subjects aged 16–40 years (Table 4). After the predicted 6MWD value for an individual was computed from this equation, the LLN could be obtained by subtracting 74 m from predicted 6MWD values. The measured 6MWD corresponded to 100 ± 8% of the predicted one. In addition, no subject showed a 6MWD <81% or <LLN.

Reliability of the single simplified equation

The mean 6MWD prospectively measured in 19 women and 20 men (mean ± SD of age, height, weight and BMI, were respectively, 28.78 ± 7.11 years, 169 ± 10 cm, 69.49 ± 13.29 kg and

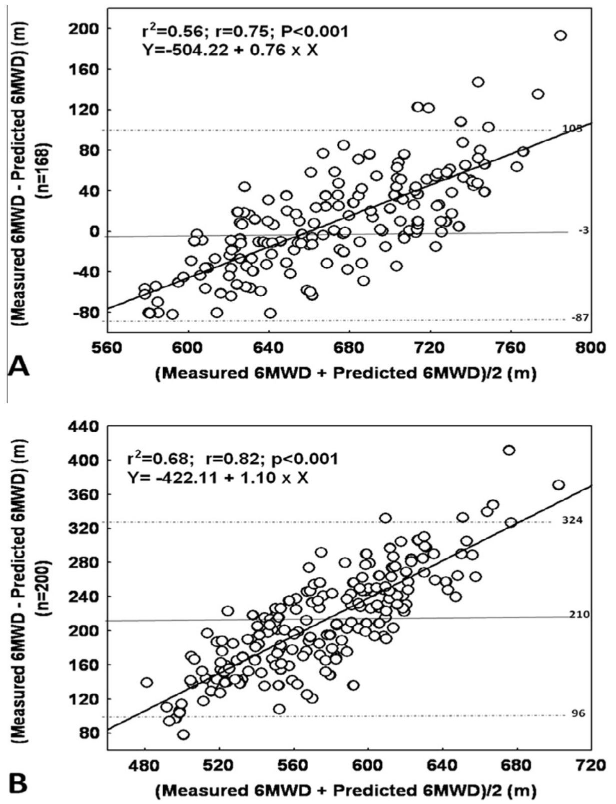

Figure 1 Bland and Altman representation, for the same age range, of measured and predicted 6-Min walk-distance (6MWD) determined from the reference equations of Chetta al. [12] (A) and Alameri et al. [11] (B). The correlation between mean difference (*Y*-axis) and mean value (*X*-axis) is significant in all instances, indicating a proportional error of 6MWD predicted with the corresponding reference equation. *r*: correlation-coefficient. r^2: determination-coefficient. *p*: probability. *n* = number of subjects of the present study in the age range. —: Mean; ····: Mean ± 1.96 SD. ----: Regression line.

24.2 ± 3.8 kg/m^2) was 686 ± 80 m, representing 101 ± 6% (range: 91–119%) of the predicted value from the retained simplified norm. The difference between prospectively measured and predicted 6MWD was not significant (5 ± 44 m, $p = 0.46$) and the correlation was significant ($r = 0.85$; $p < 0.01$). In addition, no subject showed a 6MWD <81% or <LLN.

Discussion

The 6MWD of a large group of healthy North-African subjects aged 16–40 years was prospectively measured. In addition to sex and common anthropometric data, the 6MWD appeared to be influenced by lean-mass, spirometric and physical activity data. The Saudi and Italian norms, usually applied in North-Africa, did not reliably predict 6MWD in Algerian subjects aged 16–40 years. Thus, a new single norm explaining 59% of the 6MWD variability' was established using sex, BMI, age and weight as independent predictors. Finally, in a second group of voluntary subjects prospectively evaluated, the retained norm yielded satisfactory predictions.

Given that 6MWD norms varied in function of the geographic site [26] and that the choice of the applied 6MWT norm should be specific for the country/region of origin [38], different countries need specific equations [26]. S3 Table exposes the main characteristics of the studies aiming to establish 6MWD norms and including subjects aged 16–40 years [11–24].

6MWT procedure

In a large group of healthy subjects aged 16–40 years, the expected wide range in 6MWD (550–880 m) was found, in line with similar studies (S3 Table). The average measured 6MWD (680 ± 70 m) was relatively shorter than these measured in Norwegian adults aged 18–49 years [24] and longer than those measured in other populations [11–23] (S3 Table) especially the Saudi and Italian ones [11,12] (S1 and S3 Tables). It is possible that this discrepancy reflects differences in how 6MWT protocol (encouragement, motivation aspects', corridor distance varying from 15 m [18,24] to 45 m [12,23], etc.) was conducted, applied inclusion and non-inclusion criteria, sample sizes, differences in racial, demographic and anthropometric factors (especially age ranges) of recruited adults' in each study [1,2,4,17,18]. Subjects' submaximal effort could also be considered as a possibility.

Insofar as possible, the practical factors that affect 6MWT variability [3] were controlled: 6MWT counter-indications respect, understandable information, subjects preparation, 6MWT schedule, supervisor choice, control modalities, corridor distance choice (30 m as done in other studies [11–15,17,19,20,22,23]), encouragement standardization. Like in some studies [11,13,14,17,18,23] two 6MWTs were performed. The number of 6MWTs used for familiarization purposes varied from one [20–22,24] to four [16]. These methodological precautions thus allowed us to obtain reliable results.

Subject group composition

Perfect samples are those that consist of persons randomly selected among the general population [15]. Thus, a limitation of this study, as all other studies [13–24], was the use of a convenient sample. To account for this and as done by one author [11] 84% of the sample individuals was randomized to formulate the 6MWD reference equation. The lasting 16% were enrolled in the cross-validation study of the developed reference equation. This sampling method is able of dipping the biases that are inherent to convenience sampling. In addition, as done by some authors [13–17,19–24], much effort was put into recruiting a representative sample of volunteers subjects', covering numerous economical activities and recruited from diverse settings and geographical sites in Constantine.

The calculated sample size ($n = 200$) was within the range of most earlier studies with similar aims [higher than some (from 79 [16] to 175 [19] adults) and lower than others (from 211 [21] to 617 [13] adults) (S3 Table). It is important to note that among the 617 subjects included in the multicenter study [13] only 221 were aged < 39 years. One strong point for the present study, as done by a few authors [15,22–24], was the calculation of the sample size which is a statistically crucial point [48].

Table 4 Reference equations for the 6-Min walk-distance (6MWD).

Independent variables		*B*	*P* level	Cumulative r^2	SE	LLN5%
Women (n = 100)						
Constant		347.45	0.001		140.35	66.63
BMI	(kg/m^2)	−3.68	0.002	0.219		
Height	(cm)	2.67	0.001	0.286		
Age	(Year)	−2.03	0.004	0.345		
Men (n = 100)						
Constant		2417.08	0.02		1022.35	80.73
BMI	(kg/m^2)	−41.96	0.06	0.191		
Weight	(kg)	11.63	0.09	0.210		
Height	(cm)	−8.61	0.14	0.227		
Age	(Year)	−1.24	0.16	0.243		
Total sample (n = 200)						
Constant		800.05	0.0001		22.55	74.31
Sex	(men:1/women:0)	64.71	0.0001	0.437		
BMI	(kg/m^2)	−10.23	0.0001	0.550		
Age	(Year)	−1.63	0.003	0.570		
Weight	(kg)	2.05	0.004	0.587		

B: non standardized regression coefficient. BMI: body-mass-index. DBP: diastolic-blood-pressure. FEV_1: first-second-forced-expiratory-volume. m/w: min/week. MET: metabolic-equivalent-task. *P*: probability. r^2: determination-coefficient. SE: standard-error. LLN: lower-limit-of-normal.

6MWD simplified reference equation for the total sample: 6MWD (m) = 800.05 + 64.71 × Sex − 10.23 × BMI − 1.63 × Age + 2.05 × Weight.

Interpretation: after the predicted 6MWD value from this retained equation is computed for an individual subject, for that subject the LLN may be obtained by subtracting 74.31 m.

The present study recruitment mode was comparable to those of previous studies with similar aims [11–17,19–24] (S3 Table), especially the Saudi and Italian ones [11,12] (S1 Table).

Ideally, norms are calculated with equations derived from measurements observed in a representative sample of healthy subjects in a general population [57]. Norms can also be derived from large groups of volunteers provided that criteria for normal selection and correct distribution of anthropometric characteristics are fulfilled [57]. In order to reduce the voluntary and selection bias, and as done by some authors [13,15], all included subjects were questioned so that any non-inclusion criteria would be identified. The included subjects were free from chronic diseases, although 9.5% of them showed moderate obesity or were underweight. Subjects with marked or extreme obesity were not included [11,13,17,21,24] because it is known that obese subjects with BMI > 35 kg/m^2 tend to walk slower [58] and it seems that specific 6MWD norms for obese subjects are needed [59]. In addition, 9.1% of the Algerian adults show obesity [60], and the present study group composition reflected this ''healthy'' population as they exist in the real population, increasing the external validity of the retained norms. Therefore, the present study provides helpful results for the analysis of 6MWD in North-African patients aged 16–40 years suffering from chronic diseases.

Influencing factors

The independent contributors to 6MWD in the present study population total sample were anthropometric (BMI, sex, lean-mass, age), spirometric (FEV_1) and physical activity data (Table 3). A combination of a number of these factors has been reported in previous studies including subjects aged 16–40 years [11–24]: BMI [14–16,19,20,22], sex [11,12,16,18,20,21,24], age [11–16,18–22,24], FEV_1 and FVC [14] and physical activity status [14] (S3 Table). Other anthropometric factors (eg, height [11–16,18–20,22,24] and weight [11,13,18–20,22,24]) and some Hr parameters (eg, $\%Hr_{end}$ [11] and ΔHr " = $Hr_{end\text{-}rest}$" [13]) or Borg value [11] were also reported as influencing factors (S3 Table). Other factors, not evaluated in the present study, may however have influenced 6MWD, such as socioeconomic and/or schooling levels, diet habits, leg length, quadriceps force and parity [10,31,33,61]. Anthropometric and spirometric data were largely discussed in previous papers [4,9–36,59] and the following sentences will consider the relationship between 6MWD and lean-mass, the physical activity level and Hr data.

Effect of the physical activity status on the 6MWD

Physical fitness is defined as characteristics enabling persons to perform physical activity, with the health-related components being cardiorespiratory endurance, muscle strength, muscle endurance, flexibility and body composition [24,62]. Although physical inactivity may lead to increased risk of long-term disability and co-morbidity [24,39], data about the relationship between the physical activity status and the 6MWD of healthy adults are controversial [10,11,14–16,24–26,30,31,33]. In patients with chronic diseases, there were moderate to strong relationships between 6MWD and objective measures of physical activity (r = 0.38–0.85) [1]. The 6MWD value of Algerians aged 16–40 years was 36 m greater in active subjects when compared to non-active ones. In addition, MET moderate activity was found to slightly (r = −0.18) but significantly contribute to the 6MWD variability'. The result is comparable to that found between reported physical activity [43] and measured 6MWD ($r = 0.25$) in a sample aged 13–84 years [14] or between physical activity score [63] and 6MWD ($r = 0.34$) of healthy adults aged $\geqslant$ 40 years [10]. Other studies including young adults [11,15,16] or middle-aged and elderly subjects [25,30,31,33] found no significant correlations between 6MWD and physical activity status evaluated by several ways (lower extremities exercise activity [16,40], scores of daily activity [33], self-reported physical activity including habitual walking [25,41], physical activity level [42], regular physical activity [25,31], habitual physical activity [15,43]). For example, Gibbons et al. [16] found only a tendency towards the difference between "active" and "inactive" subjects. Discrepancy between results could be explained by the different percentages of included subjects with a sedentary status or having low physical activity scores: 82% [10], 80% [11], 79% [15], 73% (present study), 52% [14], 38% [16], 25% [24]. Another explanation could be the limited capacity of the applied questionnaires' – to describe a sedentary life style in every one of its domains (e.g., amount and intensity of daily physical activity) [64]. Further studies using movement sensors are necessary.

Effect of lean-mass on the 6MWD

Although lean-mass is a predictor of exercise capacity in healthy subjects [45] no previous study aiming to establish norms in sample including healthy subjects aged 16–40 years [9–36] have evaluated its relationship with 6MWD. At the best of the authors' knowledge, the present study is the first to report a slight but significant contribution to the lean-mass in the entire group 6MWD variability': the lean-mass increase of 1 kg increases 6MWD by 1.6 m (Table 3). It is known that a higher amount of lean-mass observed in healthy whites has a major impact on the 6MWD [13]. Similarly, a heavier subject would need additional energy while ambulating to support an enlarged weight (increase in adipose tissue rather than muscle mass) and thereby curtailing the maximal level of effective work [21]. However, 6MWD was similar in COPD with and without lean-mass depletion, signifying that skeletal muscle has a limited impact on 6MWD [46]. Specific studies on the influence of lean-mass on 6MWD of healthy adults are needed.

Heart-rate response and sex-related difference

S4 Table exposes the adults Hr responses' and sex-related differences' during the 6MWT which appeared to be mainly submaximal, as reflected by a $\%Hr_{end}$ of 72% (Table 2). This finding is closer to that found in some studies [13,19] and higher than that found in others [11,12,14,15,17] (S4 Table). In contrast to some studies showing no sex-related difference neither for Hr_{rest} [13,15,19,24] nor for Hr_{end} [13,15,19,24], the present one Hr_{rest} and Hr_{end} mean values' were significantly higher in women vs. men (Table 2). This findings are similar to those found in some studies for Hr_{rest} [11–13,17,21] or for Hr_{end} [11,12,14,17,21] and confirm the sex-related differences in Hr with increase in Hr_{rest} [65,66] and in Hr_{end} [67] in women. One advanced explanation [12], was that the baroreflex Hr regulation may be different between women and men [68]. The significant positive correlation ($r = 0.16$) found between the 6MWD and Hr_{rest} data of Algerian subjects aged 16–40 years (Table 2S) is similar to that observed in Brazilian [13] or Singaporean [31] or Australian [30] populations, with significant correlations between the 6MWD and ΔHR ($r = 0.43$) [13] or $\%Hr_{end}$ ($r = 0.73$ [31], $r = 0.40$ [30], $r = 0.29$ [30]). Although the interference of Hr in the 6MWD has been suggested and considered important [11–13,30,31], only some studies [13,30,31] have considered these variables in the final 6MWD norms. Poh et al. [31] considered the $\%Hr_{end}$ in the equation as well as age, height, and weight and explained 78% of the 6MWD variability'. Jenkins et al. [30] also included the $\%Hr_{end}$ in the final equations as well as age, height and BMI and explained 0.58 and 0.61 of the Australian females and males 6MWD variability's. Britto et al. [13] considered the ΔHr in the equation as well as age, sex and height and explained 0.62 of the Brazilian 6MWD variability'. The use of Hr data as a parameter included in the 6MWD norms is controversial. The introduction of $\%Hr_{end}$ in the equation may be limited when measuring the 6MWD in subjects with low fitness levels or with cardiac impairment or medications which have an impact on mHr or when symptoms such as dyspnoea or musculoskeletal pain limit test performance [30,31]. However, according to Britto et al. [13] the ΔHr use could in part neutralize this limitation. This may happen since these diseases and medications interfere not only in the Hr_{end} but also in the Hr_{rest}, and therefore their influence on the ΔHr may be counterbalanced and diminished [13].

Choice of the appropriate 6MWD reference equation

Significant differences between measured and predicted 6MWD from the mainly applied 6MWD norms [11,12] in North-African subjects aged 16–40 years were noted (Fig. 1). While the Italian norms [12] tend to significantly overestimate the 6MWD, the Saudi ones [11] underestimate it. The implications of this for North-African subjects aged 16–40 years suffering from chronic diseases may be considerable and include potential errors relating to the level of patient disability and improbable expectations of interventions intended to improve 6MWD [10]. This argues for the application of the present study specific norms provided that the factor of altitude is taken into account (Constantine being 649 m above sea level) and confirms the international recommendation to carry on establishing regional norm [1–3,38].

Guidelines recommend that norms be derived by suitable and biologically significant statistical models taking into account the dependence of the studied data with anthropometric ones [1–3]. For only practical reasons, a single 6MWD norm including sex, BMI, age and weight as independent variables was established. This norm still explained 58.7% of the 6MWD variability, which is very acceptable compared with published norms including subjects aged 16–40 years [11–17,19–24] [r^2 varying from 0.20 [17] to 0.63 [19]] (S3 Table). In some studies [13,30,31], the mixture of anthropometric and physiological (such as ΔHr or $\%Hr_{end}$) data increases the r^2 to 0.58 [30], to 0.61 [30], to 0.62 [13] and to 0.78 [31]. Although the inclusion of such variables amplified the amount of variance explained in 6MWD, this result has limited relevance [30] since this measure is improbable to be a suitable indicator of an individual's effort intensity and is only obtainable on completion of the 6MWT [30,31].

Validation of the retained 6MWD reference equation

At the best of the authors' knowledge, among the published 6MWD norms including subjects aged 16–40 years [11–24], only few studies [11,13,14] prospectively verified their validities in a different group of healthy subjects (n = 58 [13], n = 58 [11], n = 85 [14]). The present study using additional prospective data confirmed the retained 6MWD norm' reliability.

Interpretation of measured 6MWD

In order to facilitate the calculation of the 6MWT data,the Excel software "6MWT for North-African subjects aged 16–40 years" was developed (S1 file).

In addition to the use of tables of reference centile by age-decade [23], two other approaches have been proposed to interpret subjects 6MWD values': LLN [14,19,20,22,24] or of a fixed threshold (81% [15]) below which the 6MWD is considered abnormal. In some studies [11–13,16–18,21], no interpreting method was proposed. In subjects with prior confirmation of cardiorespiratory and/or muscular diseases, a frontier low 6MWD value is more likely to be linked with disease; depending on the strength of medical evidence of disease, and the cost and consequences of a centile (LLN) is clinically suitable [47]. The present study LLN was similar to that proposed by Iwama et al. [14] and was lower than other reported values (S3 Table). Therefore, given its high reliability, the present study simplified norm is proposed to be used in North-African subjects aged 16–40 years.

Recommendations

It is essential to perform a North-African multicenter study [13,26] (with samples from Tunisia, Algeria, Morocco, Egypt and Libya) including a large sample size (1000 males and 1000 females) with a large age range (six to 90 years old) [14] and using a randomized sampling technique.

Conclusion

A reliable norm to interpret the 6MWD of healthy North-African subjects aged 16–40 years was established. The 6MWD can be simply predicted from sex, BMI, age and weight.

Conflict of interest

The authors declare they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejcdt.2015.08.003.

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