Deficiency, incapacity and social disadvantage of patients with chronic hepatitis B: a case-control study

Déficience, incapacité et désavantage social des patients atteints d'hépatite B chronique : une étude cas-témoins

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RÉSUMÉ

Introduction. Les études examinant la déficience, l'incapacité et le désavantage social des patients atteints d'hépatite virale B chronique (HVB) sont rares et présentent des conclusions contradictoires.

Objectif. Évaluer le déficit, l'incapacité et le désavantage social des patients atteints d'HVB.

Méthodes. Il s'agit d'un projet d'étude cas-témoins avec deux groupes appariés selon l'âge. Les cas (n=27) seront des patients non traités atteints d'une HVB. Les témoins (n=27) seront des participants en bonne santé. Les données suivantes seront collectées : déficit [données anthropométriques, biochimiques (fonctions rénale et hépatique, bilan lipidique, marqueurs inflammatoires), hématologiques, virologiques, de la force de préhension, et spirométriques], incapacité [distance de marche de 6 minutes (Dm6), nombre d'arrêts, saturation de l'hémoglobine en oxygène, dyspnée (échelle-visuelle-analogique), fréquence-cardiaque, tension-artérielle] et désavantage social [questionnaires «maladie chronique du foie» et d'activité-physique]. Toute donnée spirométrique < limite-inférieure-de-la normale sera considérée comme anormale. Une force de préhension <26 kg (homme) ou <16 kg (femme) sera considérée comme basse. Les signes d'intolérance à la marche seront: arrêt pendant la marche, Dm6 ≤ limite-inférieure-de-la-normale, dyspnée en fin de la marche > 5/10, baisse de la saturation de l'hémoglobine en oxygène > 5 points, fréquence-cardiaque à la fin de la marche ≤60%. Un score total d'activité-physique < 9,42 classera le participant comme sédentaire.

Résultats attendus. Par rapport aux témoins, les cas auront une altération marquée des données aérobies sous-maximales. Ces altérations aggraveront la qualité-de-vie et peuvent être liées à des anomalies musculaires et/ou spirométriques, et soutenues par une inflammation systémique et une charge virale élevée.

MOTS CLÉS

Virologie, foie, force musculaire, spirométrie, test de terrain, qualité de vie

SUMMARY

Introduction. Studies examining deficiency, incapacity and social disadvantage of patients with chronic viral hepatitis B (CHB) are scarce and present conflicting conclusions.

Objective. To assess the deficiency, incapacity and social disadvantage of patients with CHB.

Methods. This is a project of a case-control study with two age-matched groups. Cases (n=27) will be untreated patients with a CHB. Controls (n=27) will be healthy participants. The following data will be collected: deficiency [anthropometric, biochemical (renal and hepatic functions, lipid balance, and inflammatory markers), haematological, virological, handgrip-strength, and spirometric data], incapacity [6-min walk distance, number of stops, oxy-haemoglobin saturation, dyspnoea (visual analogue scale), heart-rate, and blood-pressure] and social disadvantage ["chronic liver disease" and physical-activity questionnaires]. Each spirometric data < lower-limit-of-normal will be considered abnormal. A handgrip-strength <26 kg (male) or <16 kg (female) will be considered low. The signs of walking intolerance will be: stop during the walk, 6-min walk distance ≤ lower-limit-of-normal, dyspnoea at the end of the walk> 5/10, drop in oxy-haemoglobin saturation >5 points, heart-rate at the end of the walk ≤60%. A total physical-activity score <9.42 will classify the participant as sedentary.

Expected results. Compared with controls, cases will have a marked alteration of submaximal aerobic data. These alterations will worsen quality-of-life and may be related to muscle and/or spirometric abnormalities, and supported by systemic inflammation and high viral load.

KEY WORDS

Virology, liver, handgrip strength, spirometry, field test, quality of life

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INTRODUCTION

In addition to the hepatic manifestations such as cirrhosis or hepatocellular carcinoma, chronic-hepatitis B (CHB) causes extrahepatic manifestations such as cardiovascular and pulmonary ones (1-7), which significantly aggravate the morbidity and mortality associated with CHB (8). According to the International Classification of Functioning, Disability and Disadvantage, the three stages of development (ie, deficiency, incapacity, and social disadvantage) of each chronic pathology should be systematically evaluated (9).

Many studies, which explored CHB-related deficiency, showed the extrahepatic deleterious effects of CHB on the functional state of the body at various levels [eg; loss of skeletal muscle mass, weakness of respiratory muscles, myocardial injury (2-9)]. Studies that analysed spirometric data/profile of patients with CHB are rare and report conflicting data (10, 11). First Teuber et al. (11) showed that patients with CHB (n=25) had normal forced-expiratory-volume-in-one-second (FEV_1), forced-vital-capacity (FVC), and FEV_1/FVC. Likewise, no correlation with inflammatory activity or extent of fibrosis was found (11). Second, Goh et al. (10) investigated the associations of viral hepatitis B with FEV_1, FVC, and FEV_1/FVC using multiple linear regression models adjusted for confounding factors like age, height, sex, race/ethnicity, smoking status/duration. The authors reported that patients with CHB (n=35) had significantly higher FEV_1, FVC and FEV_1/FVC (10). In practice, the handgrip strength (HS) is an indicator of an overall muscle strength, nutritional status, muscle mass, and 6-min-walk-distance (6MWD), and is a predictor of mortality, disability and surgical complications (12-14). In chronic liver diseases, measuring HS has several advantages: it assesses the nutritional status and the risk of falling, it is correlated with the muscle mass, and it is an indicator of walking speed (15-18). Moreover, a low HS is associated with non-alcoholic fatty liver disease independently of other data like socio-demographic characteristics, weight, metabolic syndrome, concomitant diseases, and lifestyle (19).

Studies which explored the incapacity related to CHB are rare (2, 3, 20, 21). It appears that only four studies have explored maximal and/or submaximal aerobic capacities of adults with CHB (2, 3, 20, 21) (Table 1). The authors of the first study investigated the submaximal aerobic capacity, and reported that compared to healthy participants (n=45), patients with a CHB (n=49) had a significantly lower 6MWD by 31 m (20). The authors of the second study investigated the maximal aerobic capacity of 26 cirrhotic patients (two of whom had a post-CHB cirrhosis) (21). They reported a positive correlation-coefficient of 0.64 between the peak oxygen uptake (VO_{2peak}) and the maximum-inspiratory-pressure (MIP), and the low quality-of-life (QOL) scores. The third study aimed to compare the strength of the respiratory muscles (MIP and maximal-expiratory-pressure (MEP)), the submaximal aerobic capacity and the QOL of patients with different aetiologies of cirrhosis (2). The authors reported that patients with post-CHB cirrhosis (n=14) compared to those with alcoholic cirrhosis (n=32) had better MIP and MEP, and had a significantly higher 6MWD by 91 m (2). Regarding QOL, out of the eight dimensions of the SF-36 questionnaire, only the “functional capacity” and the “limitation by the physical aspect” were significantly higher in the group with post-CHB cirrhosis compared to the one with alcoholic cirrhosis (2). The authors of the fourth study investigated both the submaximal and the maximal aerobic capacities (3). They aimed to test the relationship between 6MWD, MIP, VO_{2peak} and the survival rate of patients with different aetiologies of cirrhosis [post-CHB (n=16), post-chronic hepatitis C (n=40), alcoholic (n=30)] (3). They concluded that MIP, 6MWD and VO_{2peak} are predictors of mortality in patients with cirrhosis (3). In the studies where the 6-min-walk-test (6MWT) was performed (2, 3, 20), the 6MWD was expressed in absolute value. This expression mode could be a source of confusion, since it was more logical to standardize the 6MWD according to the sex and anthropometric data, which would allow a better comparison between the different groups (22).

Health-related QOL and behaviours (eg, physical-activity) are important for the management of chronic medical conditions (23). Regarding social disadvantage, many studies explored the QOL of patients with CHB at different stages of the disease (24, 25). Despite the diversification of the used questionnaires, the majority of studies confirmed the deterioration of QOL of patients with CHB. However, the use of a generic QOL questionnaire [eg, SF-36 (24) applied in some studies (2, 21)] is open to criticism, since there are specific QOL questionnaires to liver diseases, including the “chronic liver disease questionnaire” (CLDQ) (26), which was validated in patients with CHB (27). It seems that 50% of patients with CHB are physically-inactive (28). Physical-activity is among the most critical behavioural determinants of health (29). From a public health standpoint, it is vital to determine the level of

physical-activity in order to provide a theoretical basis for the expansion of suitable guidelines to turn aside the problems related to physical-inactivity (30). Therefore, studies raising the impacts of CHB on physical-activity are interesting (28). However, such studies are scarce (28), and often applied a non-specific questionnaire (31). For example, in a Korean study (28), physical-inactivity was defined as the performance of a moderate-to-vigorous physical-activity <150 min/week (31). It was more reasonable to use a specific questionnaire like the Voorrips questionnaire (32) which allows the calculation of scores related to three types of physical-activity: daily, sports, and leisure activities.

To the best of the authors' knowledge, no study has simultaneously explored the aforementioned three stages of development in a single and homogeneous group of patients with non-cirrhotic CHB. In addition, the four studies analysing the maximal and/or submaximal aerobic capacities of patients with CHB (2, 3, 20, 21) had a major methodological limitations related to the studied populations. Indeed, only one study included patients with non-cirrhotic CHB (20), and the other three studies included cirrhotic patients of different aetiologies including post-CHB (2, 3, 21). This approach could be a source of confusion, since the clinical outcomes are different. Taking into account the aforementioned points, there are two objectives for this case-control study (case: patients with non-cirrhotic CHB; control: healthy participants). The main objective is to compare data of the two groups while respecting the three evolutionary stages of any chronic disease: i) Deficiency: anthropometric, biochemical, haematological, spirometric, and HS data; ii) Incapacity: 6MWT data; and iii) Social disadvantage: CLDQ and physical-activity questionnaires data. The second objective is to assess, in patients with CHB, the correlations between 6MWD, and biological, spirometric, HS, QOL and physical-activity data.

POPULATION AND METHODSSTUDY DESIGN

This work is a protocol of a case-control study that will be carried out in collaboration with four departments (ie, physiology and functional explorations, infectious diseases, biochemistry and haematology laboratories (Farhat HACHED hospital, Sousse, Tunisia)). The approval of the hospital medical and research ethics committee (approval N° 3010/2020) was obtained. All participants will receive a report of their explorations.

Study population and protocol

Two groups of participants will be included. Cases will be patients with a CHB and controls will be healthy participants. The recruitment methods, the inclusion and non-inclusion criteria are detailed in the Box 1. The study consists of a single visit where a maximum of three participants will be explored in the morning between 8 a.m. and noon. Figure 1 details the study protocol. When welcoming participants, an information sheet will be issued and an informed consent will be signed.

Box 1. Chronic-hepatitis B (CHB) diagnosis, and applied inclusion, non-inclusion and exclusion criteria.

	Cases	Controls
CHB diagnosis	.Viral activity: assessed through a-DNA-hepatitis B virus test. .Analysis: COBAS® TaqMan® HIV-1 analyser. .Virological exam: done 3 to 4 months before the patient inclusion in the study in order to determine the viral load **(33)**.	
Recruitment method	.Patients followed at the outpatient clinic infectious diseases	.Caregivers of patients with a CHB .Relatives of persons involved in the study .An advertisement to recruit healthy participants will be launched via the personal Facebook account of the 1st author
Inclusion criteria	.Age: 30 to 50 years .CHB diagnosed with a surface antigen persisting for at least 6 months before inclusion in the study .AgHBe positive or negative with a viral load > 2000 IU/ml **(33)** .No comorbidities .No co-infection with other viruses .No liver damage .No indication of treatment [fibroscan score 0-6, and/or score at the liver biopsy puncture (activity and fibrosis) <2] .No physical/mechanical problem	.Age: 30 to 50 years .Healthy participant .No chronic diseases .No physical/mechanical problem .No alcohol intake
Non-inclusion criteria	.6-min-walk-test contraindications **(32)**: signs of unstable angina or myocardial infarction during the previous month, resting heart-rate≥ 120 bpm, systolic-blood-pressure≥ 180 mmHg, diastolic-blood-pressure≥ 100 mmHg .History of orthopaedics/rheumatologic conditions which may interfere with the walking or handgrip-strength .Systemic impairment which may influence blood test results (***eg***; diabetes-mellitus or renal-failure)	
Exclusion criteria	.Loss of certain biological data .Incomplete performance of the 6-min-walk-test and/or spirometric test	

Table 1. Studies analysing the aerobic fitness of patients with chronic hepatitis B: methodology and results.

1st author (ref)	Alameri (20)	Galant (21)	Galant (2)	Faustini Pereira (3)
Study duration	.12 months	.5 months	.5 months	.3 years
City (Country)	.Riyad (Saudi Arabia)	.Porto Alegre (Brazil)	.Porto Alegre (Brazil)	.Porto Alegre (Brazil)
Main aims	.To compare the 6MWD of healthy participants and patients with hepatic pathologies .To study the correlations between the 6MWD and certain clinical and biochemical markers of the disease	.To assess the correlation between **V**O_{2peak}, and respiratory muscle strength and QOL in patients with hepatic cirrhosis	.To compare the muscle strength, exercise capacity and QOL data of 3 groups of patients with cirrhosis	.To evaluate the relationship between the 6MWD, MIP, VO_{2peak} and the survival rate of patients with cirrhosis
Study design	.Prospective study	.Cross-sectional study	.Cross-sectional study	.Prospective study
Sample (M/F)	.250 (150/100)	.26 (14/12)	.86 (64/22)	.86 (66/20)
Populations	**4 groups** **.GA**: 45 (22 M) healthy **.GB**: 49 (22 M) CHB **.GC**: 58 (42 M) CHC **.GD**: 98 (64 M) cirrhosis	**3 groups (cirrhosis)** **.GA**: 2 post-CHB **.GB**: 16 post-CHC **.GC**: 8 post-alcohol	**3 groups (cirrhosis)** **.GA**: 40 (30 M) post-CHC **.GB**: 14 (10 M) post-CHB **.GC**: 32 (20 M) post-alcohol	**3 groups (cirrhosis)** **.GA**: 40 post-CHC **.GB**: 16 post-CHB **.GC**: 30 post-alcohol
Characteristics of patients with CHB	.Ag HBs+ .ALT: normal or increased .Bilirubin, albumin, INR: normal .CBC: normal .Abdominal echography: normal .No PH or cirrhosis	.NR	.NR	.No systemic disease .No co-infection .No chronic disease
Age (years)	**GB:** 18-80[a], 38±12[b]	.**TS**: 53±9[b]	**GB:** 52±6[b]	.< 65, **TS**: 56±8[b]
Height (m)	.NR	.NR	**GB:** 1.69±0.73[b]	.**TS**: 1.67±0.83[b]
Weight (kg)	.NR	.NR	**GB:** 69±11[b]	.**TS**: 67±9[b]
BMI (kg/m²)	.**GB:** 33.3±20.6[c]	.**TS**: 25.4±2.25[c]		.**TS**: 24.10±1.21[b]
Applied tests (main collected data)				
Deficiency	.NA	.Respiratory muscle strength: MIP/MEP (cmH_2O)	.Spirometric data: FEV_1, FVC .Respiratory muscle strength: MIP/MEP (cmH_2O)	.Respiratory muscle strength: MIP/MEP (cmH_2O)
Incapacity	.6MWT: 6MWD (m), HR (bpm), oxy-sat (%), dyspnoea (Borg scale)	.CPET: VO_2peak (mL/min/kg), dyspnoea (Borg scale)	.6MWT: 6MWD (m), HR (bpm), oxy-sat (%), RR (cpm), dyspnoea (Borg scale)	.6MWT: 6MWD (m), oxy-sat (%), HR (bpm) .CPET: VO_2peak (mL/min/kg)
Social disadvantage	.NA	.QOL: SF-36	.QOL: SF-36	.NA
Other data	.Biological data (ALT, AST, GGT, AP, haemoglobin, albumin, bilirubin, creatinine)	.MELD: disease severity score	.MELD: disease severity score	.Survival rate
Main results				

Deficiency	.NA	.MIP: 73±22[b] .MEP:79±29[b]	.MIP: GA: 82±14[b], GB: 72±7[b], GC: 66±11[b] .MEP: GA: 83±12[b], GB: 82±14[b], GC: 65±11[b] .FEV_1 (%): GA: 91±17[b], GB: 89±18[b], GC: 87±14[b] .FVC (%): .GA: 95±19[b], GB: 97±17[b], GC: 93±30[b]	.MIP: =70±14[c], < 70: SRof 62%, ³ 70: SRof 93%, AUC ROC, sensibility and specificity: 0.69/71%/53%, SR 18% more higher with MIP increase
Incapacity	.6MWD: GA: 421±47[b], GB: 390±53[b], GC: 357±72[b] GD: 306±111[b] .HR_{end} (bpm): GB: 86±13[b] .Oxy-sat_{end} (%): GB: 98.2±0.76[b] .$Dyspnoea_{end}$: GB: 0.53±0.73[b]	.VO_2peak: 17.01±5.91[b]	.6MWD: GA: 476±29[b], GB: 464±32[b], GC: 373±50[b] .HR_{rest} (bpm): GB: 77±11[b] .HR_{end} (bpm): GB: 91±15[b] .RR_{rest} (cpm): GB: 15±3[b] .RR_{end} (cpm): GB: 21±3[b] .Oxy-sat_{rest} (%): GB: 98±1[b] .Oxy-sat_{end} (%): GB: 97±1[b] .$Dyspnoea_{rest}$: GB: 1±0,6[b] .$Dyspnoea_{end}$: GB: 2±1[b]	.6MWD: 410±29[b], < 410: SRof 55%, ³ 410: SRof 97%, AUCROC, sensibility and specificity: 0.87/92%/31%, SR 20% more higher with 6MWD increase V.O_2peak: =17.06[c], < 17: SRof 55%, ³17: SRof 94%, AUCROC, sensibility and specificity: 0.78/87%/41%, SR 30% more higher with VO_2pic increase
Social disadvantage	.NA	.SF-1=47±26[b], SF-2=35±38[b], SF-3=49±24[b], SF-4=42±18[b], SF-5=48±28[b], SF-6=61±31[b], SF-7=51±42[b], SF-8=58±30[b]	.SF-1=65±22[b], SF-2=65±21[b], SF-3=61±26[b], SF-4=52±18[b], SF-5=63±26[b] SF-6=71±25[b], SF-7=52±15[b], SF-8=68±16[b]	.NA
Other results	6MWD correlated with .Age (r=-0.482) .Height (r=0.281) .Dyspnoea [$_{rest}$ (r=-0.518), $_{end}$ (-0.581)] .Haemoglobin (r=0.373) .Albumin (r=0.311)	VO_{2peak} correlated with: .MIP (r=0.64) .MELD (r=0.91)	6MWD correlated with: .MELD (r=-0.56)	Mortality .GA: 3 .GB: 5 .GC: 11
Conclusion	.The 6MWT is useful for assessing the physical capacity of patients with chronic liver disease.	.There is a correlation between the VO_{2peak} and MIP. .Patients have poor QOL	.Compared to patients with cirrhosis post-alcoholic, those with cirrhosis post-CHB have better respiratory muscle strength, better exercise capacity, and better QOL.	.6MWD, MIP, VO_{2peak}: predictors of mortality in patients with cirrhosis

ALT: alanine-aminotransferase. **AP**: alkaline-phosphatase. **AST**: aspartate-aminotransferase. **AUC**: Area-under-the-curve. **C**: chronic-hepatitis B. **CHB:** chronic-hepatitis B. **CHC**: chronic-hepatitis c. **CPET**: cardiopulmonary-exercise-test. $_{end}$: end of the 6MWT. **F**: female. **FEV_1**: forced expiratory-volume-in-one-second. **FVC**: forced-vital-capacity. **G**: group. **GGT**: gamma-glutamyltranspeptidase.**HR**: heart-rate. **INR**: international-normalized-ratio. **M**: male. **MELD**: disease-severity-score. **MEP**: maximal-expiratory-pressure. **MIP**: maximal-inspiratory-pressure. **NA**: non-applied. **NR**: non-reported. **Oxy-sat**: oxygen haemoglobin saturation. **PH**: portal-hypertension. **QOL**: quality-of-life. **r**: coefficient of correlation. $_{rest}$: at rest before the 6MWT. **ROC**: receiver-operating-characteristic. **RR**: respiratory-rate. **SF-1**: functional-capacity.**SF-2**: limited by the physical aspect. **SF-3**: pain. **SF-36**: short form-36. **SF-4**: general health. **SF-5**: vitality.**SF-6:** social. **SF-7**: mental health. **SF-8**: limitation by emotional aspects. **SR**: survival rate. **TS**: total-sample. VO_{2peak}: peak of oxygen consumption. **6MWD**: 6-min-walk-distance.**6MWT**: 6-min-walk-test.

Date were expressed: [a]Minimum-maximum; [b]Mean±standar-deviation, [c]Mean.

Study of Alameri:

GB: younger than GC or GD

6MWD of GB: lower than this of GA, higher than these of GC and GD

Study of Galant-2012:

FEV_1 and FVC of GB: similar to other 2 groups

MIP and MEP of GB: higher than these of GC.

6MWD of GB: higher than this of GC.

HR_{end} of GB: lower than this of GC.

$Dyspnoea_{end}$ of GB: lower than this of GC.

SF-1 and SF-2 scores of GB: higher than these of GC.

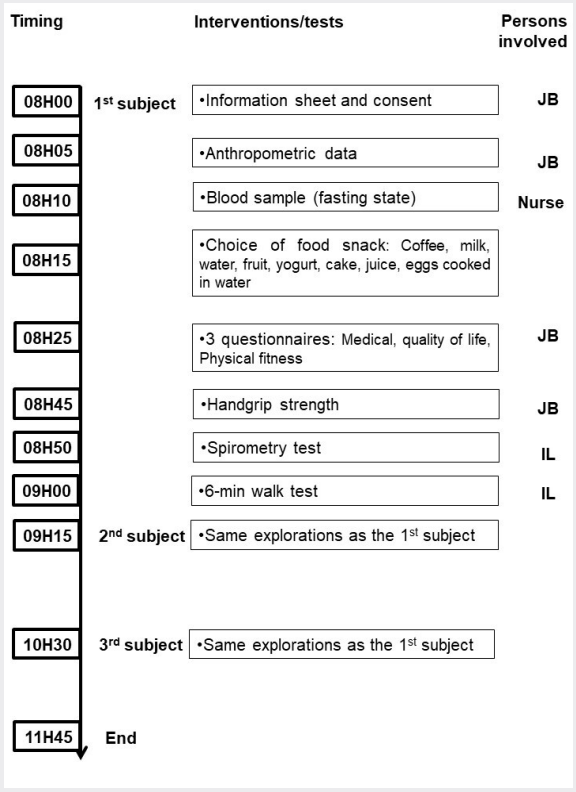

Figure 1. Study protocol.

Sample size

The sample size was estimated using this formula **(35)**: $N = ((r+1) (Z_{\alpha/2} + Z_{1-\beta})^2 s^2)/(rd^2)$.

• "$\boldsymbol{Z_{\alpha/2}}$" is the normal deviate at a level of significance = 1.96 (5% level of significance);

• "$\boldsymbol{Z_{1-\beta}}$" is the normal deviate at 1-β% power with β% of type II error (1.28 at 90% statistical power);

• "r" (= n_1/n_2, n_1 and n_2 are the sample sizes for the cases and controls groups, such $N = n_1 + n_2$) is the ratio of sample size required for two groups (r = 1 gives the sample size distribution as 1:1 for two groups);

• "s" and "d" are the pooled standard-deviation (SD) and difference of 6MWD means of two groups. These two values were obtained from a previous case-control study aiming to compare the 6MWD of 48 patients with CHB with that of 45 healthy participants (20). Controls and cases had 6MWD means of 421 and 390 m, respectively, with a mean SD of 50 m.

The injection of the aforementioned data into the formula results in a total sample of 54 participants (27 in each group). The assumption of 10% loss of some biological data gives a revised sample of 60 participants (=54/(1-0.10)).

CHB diagnosis

The CHB diagnosis criteria **(33)** are detailed in **Box 1.**

Data collection procedures, and applied definitions

Clinical, sociodemographic and socioeconomic data will be collected using a standard medical questionnaire, which is widely used in hospital departments (Appendix/ Section A). The questions, which will be asked in Arabic, are essentially closed-ended and most often dichotomous questions. The socioeconomic-level will be determined according to the participant profession (36) and two levels will be defined (unfavourable/favourable). Two schooling-levels will be defined arbitrarily [low (illiterate/primary school); high (secondary/university)]. Cigarettes smoking will be evaluated in pack-years and participants will be classified into two groups (non-smoker: <5 pack-years; smoker: >= pack-years). Depending on alcoholic habit, participants will be classified into two groups (consumer/ non-consumer).

Sex and age (years) will be noted, and height (cm) will be measured. Body composition [weight (kg), body mass index (BMI, kg/m^2), muscle mass rate (%), body fat rate (%), water percentage (%), bone mass (kg)] will be measured and/or calculated using a bioelectric impedancemeter [Beurer (BF-600, Beurer GmbH, Germany)]. According to the BMI, four corpulence statuses will be identified: leanness (BMI <18.5 kg/m^2), normal weight (BMI: 18.5-24.0 kg/m^2), overweight (BMI: 25.0-29.9 kg/m^2), and obesity (BMI ≥30 kg/m^2).

Blood samples will be taken on serum tubes from peripheral venous blood and will be sent to the biochemistry and haematology laboratories. The blood will be collected using a 20-ml syringe and will be divided into four tubes [*ethylene-diamine-tetra-acetic*, *citrat*, *fluoride*; *lithium heparin,* and *dry tubes*]. The usual techniques of the two laboratories will be used to determine the values of each biological data. The haematological and biochemical data that will be determined/calculated and the definitions that will be applied (5, 37-40) are detailed in Boxes 2 and 3, respectively.

Box 2. Haematological data, erythrocyte-sedimentation-rate (ESR) and applied definitions.

Tubes	Data	Normal values	Applied definitions	Ref
EDTA	Haemoglobin	**M**: 14-17 g/dL **F**: 12-16 g/dL	Anaemia: haemoglobin < 12 (**F**) or< 14 (**M**) Polycythaemia: haemoglobin > 17	**(40)**
	Erythrocytes	4.2-5.9 10^6/mm^3	Low: erythrocytes < 4200000	**(40)**
	Leucocytes	4.5-11 10^3/mm^3	Leukopenia: leucocytes < 4500 Leucocytosis: leucocytes > 11000	**(40)**
	Neutrophils	2.6-8.5 10^3/mm^3	High: neutrophils > 8500	**(40)**
	Eosinophils	0-0.55 10^3/mm^3	High: eosinophils > 550	**(40)**
	Basophils	0-0.22 10^3/mm^3	Basocythemia: basophils> 220	**(40)**
	Lymphocytes	0.77-4.5 10^3/mm^3	Lymphopenia: lymphocytes < 770	**(40)**
	Monocytes	0.14-1.3 10^3/mm^3	Monocytosis: monocytes > 1300	**(40)**
	Thrombocytes	150-350 10^3/mm^3	Thrombocytopenia: thrombocytes < 150000 Thrombocytosis: thrombocytes > 350000	**(40)**
	ESR- 1st hour	**M**: 0-15 mm **F**: 0-20 mm	Biological inflammatory syndrome: ESR> 15 (**M**) or > 20 (**F**)	**(40)**
Citrate	Prothrombin-level	70-100%	Low: prothrombin-level < 70%	**(37)**

EDTA: ethylene-diamine-tetra-acetic. **F**: female. **M**: male.

Box 3. Biochemical data, C reactive protein (CRP), and applied definitions

Tubes	Function	Data	Normal values	Applied definitions	Ref
Fluoride	Renal function	Urea	0.15-0.50 g/L	High: urea> 0.50	**(38)**
		Creatinine	7-13 mg/L	High: creatinine > 14	**(38)**
Lithium heparin	Liver function	AP	36-150 UI/L	High: AP> 150	**(40)**
		ALT	0-35 UI/L	Cytolysis: ALT > 35	**(40)**
		AST	0-35 UI/L	Cytolysis: AST > 35	**(40)**
		Total-bilirubin	0.3-1.2 mg/dL	High: bilirubin > 1.2	**(40)**
		Conjugated-bilirubin	0-0.3 mg/dL	High: bilirubin > 0.3	**(40)**
		GGT	8-78 UI/L	High: GGT > 78	**(40)**
		Albumin	35-54 g/L	Low: albumin < 35	**(40)**
Dry tube	Lipid panel	TC	3.88-5.15 mmol/L	High: TC > 5.15	**(40)**
		TG	< 2.82 mmol/L	High: TG > 2.82	**(40)**
		HDL-C	≥ 1.04 mmol/L	Low: HDL-C < 1.04	**(40)**
		LDL-C (=TC-HDL-C - TG/5)	≤ 3.36 mmol/L	High: LDL-C > 3.36	**(40, 41)**
Lithium heparin	Others	UA	0.15-0.47 mmol/L	High: UA> 0.47	**(40)**
		CRP	< 5 mg/L	Biological inflammatory syndrome: CRP>12	**(39)**
		CPK	30-170 U/L	Myolysis: CPK > 170	**(40)**
Fluoride		Fasting-glycaemia	3.9-5.8 mmol/L	High: glycaemia> 5.8 Low: glycaemia< 3.9	**(40)**

ALT: alanine-aminotransferase. **AP**: alkaline-phosphatase. **AST**: aspartate-aminotransferase. **CPK**: creatine-phosphokinase. **GGT**: gamma-glutamyl-transpeptidase. **HDL-C**: high-density-lipoprotein-cholesterol. **LDL-C**: low-density-lipoprotein-cholesterol. **TC**: total-cholesterol. **TG**: triglycerides. **UA**: uric-acid.

The upper-limb muscle strength will be measured using an adjustable handle digital HS dynamometer (TKK5401®, Takei Scientific Instruments Co., Ltd., Niigata, Japan). This reliable and valid dynamometer has a measuring range of 5 to 100 kg of force, with increments of 1 kgf (42). Participants will have a brief demonstration and verbal instructions for the test, and if necessary, the dynamometer will be adjusted to the size of the hand. The measurement will be taken in a standing position with the shoulder adducted and in neutral rotation, and the arms parallel but not in contact with the body. Participants will be asked to tighten the dynamometer as hard as possible, while exhaling. The test will be repeated three times for each hand. The highest values obtained will be used for the evaluation of the maximum-voluntary strength. The HS will be expressed as an absolute value (kg) and any value <26 kg (male) or <16 kg (female) will be considered low (43).

Spirometry will be performed using a portable spirometer (SpirobankG MIR via del Maggiolino 12500155 Rome, Italy) according to the international recommendations (44). The following data will be noted: FEV_1 (L, %), FVC (L, %), FEV_1/FVC (absolute value), maximal mid-expiratory-flow (L/s, %). Local spirometric norms will be used (45) and any spirometric data< lower-limit-of-normal (LLN) will be considered low (46). The obstructive-ventilatory-defect will be defined as FEV_1/FVC <LLN (46).

The submaximal aerobic capacity will be evaluated via the 6MWT. Participants will be asked to wear comfortable clothing and appropriate footwear for walking, to come on an empty stomach, and finally not to perform strenuous exercise in the two-hours preceding the 6MWT (34). A single 6MWT will be performed in a 40 m flat corridor. The instructions given before the 6MWT will correspond to those recommended by the international guidelines (34). Walking will be stopped if the participant experiences chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis, and a pale or ashen appearance (34). Heart-rate (bpm), oxy-haemoglobin saturation (Oxy-sat, Handheld pulse oximeter M700, Biolight CO., LTD. China), blood-pressure and dyspnoea, will be measured and/or assessed for a participant sitting in a chair before ($_{rest}$) and immediately at the end ($_{end}$) of the 6MWT. The maximal predicted heart-rate will be calculated [= 208 - 0.7 × Age] (47). The following 6MWT data will be noted, measured or calculated: 6MWD (m, %), number of stops while walking, heart-rate (bpm, %), Oxy-sat (%) and ΔOxy-sat (=$Oxy\text{-}sat_{end}$ - $Oxy\text{-}sat_{rest}$), dyspnoea and blood-pressure. Dyspnoea will be assessed via the visual-analogue-scale rated from 0 (no shortness of breath) to 10 (maximum shortness of breath) (48). North-African 6MWD norms will be used and 6MWD LLN will be calculated (22, 49). The following definitions will be applied (22, 36, 46):

· Signs of walking intolerance: 6MWD<LLN, stop while walking, $dyspnoea_{end}$> 5/10;

· Clinically significant desaturation: ΔOxy-sat> 5 points

· Chronotropic insufficiency: $heart\text{-}rate_{end}$<60%

The CLDQ is a specific questionnaire(26) validated in patients with a CHB(27). This short and easy-to-administer questionnaire correlates with the severity of the disease(26). The CLDQ, which is intended to find out how the patients felt during the last two weeks, includes 29 questions with the choice of only one answer among seven (1: all the time; 2: most of the time; 3: a good bit of the time; 4: some of the time; 5: a little of the time; 6: hardly any of the time; 7: None of the time). The questions are divided into six areas: Abdominal Symptoms (questions 1, 5, 17); Fatigue (questions 2, 4, 8, 11, 13); Systemic Symptoms (questions 3, 6, 21, 23, 27); Activity (questions 7, 9, 14); Emotional Function (questions 10, 12, 15, 16, 19, 20, 24, 26); and Worry (questions 18, 22, 25, 28, 29). The overall CLDQ score, which is calculated by adding all the answers chosen, can range from 0 to 203. A high score corresponds to a poor QOL (26). The CLDQ was translated into Tunisian dialect by the research team (Appendix/Section B). To ensure a good translation, a role-play between the principal investigators was performed.

The level of physical-activity will be estimated by the Voorrips questionnaire (32). This questionnaire is reproducible and its score is positively correlated with the 24-hour measurement of the physical-activity quantified by the use of a pedometer (32). The Arabic version (Appendix/Section C) is invalidated but widely used in previous studies (50). This questionnaire includes 51 questions divided into three parts, each evaluating a different score for three types of physical-activity: daily, sports and leisure activities. The sum of the three scores represents the total-physical-activity score. According to this last score, two groups of participants will be defined: [sedentary (score <9.42); active (score ≥ 9.42)] (32).

Statistical analysis

The analysis of the distribution of quantitative data will be performed using the Kolmogorov-Smirnov test. When

the distribution will be normal and the variances will be equal, the results will be expressed by their means±SD. Otherwise, the results will be expressed by their medians (interquartiles). Categorical data will be expressed as numbers (%). Student's T and/or Mann-Whitney U tests will be used to compare quantitative data from the two groups. The Chi-square test will be used to compare the percentages of participants between the two groups. Student's T test will be used to analyse the associations between the measured 6MWD (m) and the patients' categorical data. The correlation-coefficient will be used to analyse the associations between the 6MWD and the quantitative data of the deficiency (biological, spirometric and HS data) or the scores of QOL and physical-activity. To assess the 6MWD influencing factors, the authors intend to establish a linear multiple regression. Only the significantly associated independent data, in the previous step, will be included in this regression. All statistical procedures will be performed using a Statistica statistical software (StatSoft, Inc. (2011). STATISTICA, version 12). Significance will be set at the 0.05 level.

EXPECTED RESULTS

CHB is believed to "alter" spirometric data, HS, submaximal aerobic capacity and QOL. In this context, in front of patients newly diagnosed with CHB, it will be desirable to systematically explore the three stages of the chronic evolution of their disease, namely deficiency (HS and spirometry), incapacity (6MWT) and social disadvantage (questionnaires of QOL and/or physical-activity) and seek the impact of the incapacity on the QOL. The final outcome expected from the results of this protocol is twofold: ***i)*** integrate HS, spirometry and 6MWT as means of evaluating the progress report of patients with CHB in order to assess the independence level of the patient during the daily living activities; and ***ii)*** put forward physiopathological arguments reinforcing the role of cardio-respiratory rehabilitation in the therapeutic management of CHB.

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Appendix 1. MEDICAL QUESTIONNAIRE
SECTION A. GENERAL QUESTIONNAIRE (IN FRENCH)

Identification
1. Nom:……..**2.** Prénom:……**3.** Date de naissance:…../……/……**4.** Origine: …….
5. Niveau de scolarisation: 1. Analphabète 2. Ecole primaire 3. Ecole secondaire 4. Universitaire 5. Autres
6. Statut professionnel: 1. En exercice 2. Retraité
7. Profession actuelle ou antérieure: 1. Artisan 2. Commerçant 3. Cadre et profession intellectuelle supérieure 4. Profession intermédiaire 5. Ouvrier 6. Agriculteur exploitant 7. Sans activités 8. Autres
Caractéristiques de l'hépatite virale B (pour les malades uniquement)
8. Date de découverte (année):……**9.** Traitements: 0. Non traité…… 1. Traité:……
10. Coïnfection virale: 0. Non 1. Oui ……**11.** Charge virale:……u/ml
12. Fibrosanner: 0. Non 1. Oui……**13.** Si oui à la question 12: score:……
14. PBF: 0. Non 1. Oui ……**15.** Si oui à la question 14: score:……
Antécédents personnels
16. Maladie respiratoire: 0. Non 1. Oui; Si oui passer aux questions 17 et 18
17. Signes/symptômes/pathologie: 1. Toux > 3 mois par an 2. Toux productive > 3 mois par an 4. Tuberculose 8. Fibrose interstitielle diffuse, 16. Syndrome d'apnée de sommeil 32. Dyspnée d'effort ≥ niveau 2 64. Asthme 128. Atopie 256. BPCO 512. autres……
18. Traitement en cours 0. Aucun 1. Broncho-dilatateurs 2. Corticoïde 4. Muco-modificateurs 8. Antitussifs 16. Analeptique 32. Antituberculeux 64. Autres…….
19. Maladie cardiovasculaire: 0. Non 1. Oui; Si oui passer aux questions 20 et 21
20. Pathologie 1. Angine de poitrine 2. Infarctus du myocarde 4. Insuffisance cardiaque 8. Trouble du rythme cardiaque 16. Artérite des membres inférieurs 32. Autres……..
21. Traitement 0. Aucun 1. Dérivé nitré 2. Anti-arythmique 4. Inhibiteur calcique 8. Anti-ischémique 16. Digitalique 32. Bêtabloquant 64. Antiagrégant plaquettaire 128. Inhibiteur de l'enzyme de conversion 256.Anti-vitamine K 512. Autres……
22. Hypertension artérielle: 0. Non 1. Oui ; Si oui, passer aux questions 23-25
23. Ancienneté (année):……**24.** Stabilité: 0. Stable 1. Instable
25. Traitements en cours 1. Régime 2. Bêtabloquants 4. Antihypertenseur central 5. Inhibiteur calcique 6. Diurétique 7. Inhibiteur de l'enzyme de conversion 8. Vasodilatateur 9. Autres……
26. Avez-vous une dyslipidémie? 0. Non 1. Oui ; Si oui passer à la question 27
27. Traitements:1. Régime 2. Hypolipémiant
28. Avez-vous un diabète? 0. Non 1. Oui…**29.** Avez-vous une anémie? 0. Non 1. Oui **30.** Avez-vous une dysthyroïdie? 0. Non 1. Oui
31. Avez-vous un néoplasie? 0. Non 1. Oui **32.** Avez-vous une maladie systémique? 0. Non 1. Oui
33. Hospitalisations médicales antérieures ; Si oui, passer aux questions 34 et 35
34. Services 1)…….. … 2)…… … ……3)…… ……**35.** Diagnostics 1)……..2)…… 3)……..
36. Antécédents chirurgicaux: 0. Non 1. Abdomino-pelviens 2. Urologiques 4. Thoraciques 8. Orthopédiques 16. Neurochirurgicaux 32. Autres:…
37. Nombre de grossesses menées à terme,nombre d'avortements, nombre d'enfants: / /
Habitudes et mode de vie
38. Avez-vous fumé des cigarettes? 0. Non 1. Oui , Si oui, passer aux questions 39 et 40
39. Nombre de cigarettes par jour/an:……**40.** Si vous avez arrêté de fumer, depuis quand (années):……
41. Fumez-vous la chicha? 0. Non 1. Oui ; Si oui, passer à la question 42
42. Nombre de chicha par jour/an: ……**43.** Consommation d'Alcool: 0. Non 1. Oui

SECTION B. CHRONIC LIVER DISEASE QUALITY OF LIFE QUESTIONNAIRE (CLDQ) (IN ARABIC)

استبيان مرض الكبد المزمن - (CLDQ) جودة مؤشر الحياة للمرضى الذين يعانون من مرض الكبد المزمن

تم تصميم هذا الاستبيان لمعرفة كيفاش كان شعورك خلال الأسبوعين الماضيين. سيتم سؤالك عن الأعراض المرتبطة بمرض الكبد، كيفاش تأثرت في القيام بالأنشطةاليومية، و كيفاش كان تأثيرها على حالتك المزاجية. يرجى استكمال جميع الأسئلة وتحديد إجابة واحدة فقط لكل سؤال.

السؤال: في الجمعتين اللي تعداو قداش من مرة	ديما	معضم الوقت	ساعات	القليل من الوقت	دوب من بلاش	تقريبا أبدا	أبدا
1. حسيت بقلق منع نفاخ في كرشك؟							
2.حسيت روحك تاعب؟							
3.حسيت بوجيعة في بدنك؟							
4.جاك النوم و مازال الليل ماجاش؟							
5.جاتك وجيعة في كرشك؟							
6. حسيت بضيق النفس سبّبك قلق في أعمالك اليومية؟							
7. ما نجمتش تاكل كمية الماكلة اللي حبيت تاكلها؟							
8.تقلّقت على خاطر فرنك قاعدة تنقص؟							
9. لقيت مشكلة بش تهز والا تحرك حاجة رزينة؟							
10.حسيت روحك متقلق و مش قد بعضنك؟							
11. حسيت بالفشلة وقلة الجهد؟							
12. حسيت روحك مش فرحان؟							
13. حسيت روحك ناعس؟							
14.تقلّقت على خاطر ماكنتك محدودة؟							
15.حسيت روحك فيسع تتنرفز؟							
16.لقيت صعوبة بش ترقد في الليل؟							
17.حسيت بقلق وعدم راحة في كرشك؟							
18.حيرك من تأثير مرض كبدتك على عائلتك؟							
19.حسيت روحك فيسع تتقلب و كل ساعة و علمها؟							
20.ماتجمتش ترقد فيسع في الليل؟							
21.تدتك الكرمب (تكبيشة)؟							
22.خفت لا الأعراض اللي عندك تطور لمشكلة أكبر؟							
23. حسيت ريقك شايح؟							
24. حسيت بالاكتئاب؟							
25. اتقلقت لا حالتك تزيد تتدهور؟							
26. لقيت عندك مشكلة في التركيز؟							
27. عانيت من الحكة في بدنك؟							
28. خفت لا حالتك معادش تتحسن؟							
29.تجيرت في صورة ما إذا إستحقيت زرع كبد زعما تلقى والّا لا؟							

SECTION C. VOORRIPS PHYSICAL ACTIVITY QUESTIONNAIRE (IN ARABIC)

I.الأنشطة اليومية داخل المنزل
1) هل تقوم بالأعمال المنزلية الخفيفة؟ (غسيل الأواني، إزالة الغبار، خياطة الملابس، إلخ..)
0. لا (أقل من مرة في الشهر)
1. أحيانا (فقط عندما لا يمكن لقريني أو لطرف ثالث القيام بها)
2. غالب الوقت (بعون من قريني أو طرف ثالث).
3. دائما (وحدي أو مع قريني)
2) هل تقوم بالأعمال المنزلية المجهدة؟ (تنظيف الأرضية و الشبابيك،اخراج سلة المهملات،إلخ..)
0. لا (أقل من مرة في الشهر)
1.أحيانا (فقط عندما لا يمكن لقريني أو لطرف ثالث القيام بها)
2.غالب الوقت (بعون من قريني أو طرف ثالث).
3. دائما (وحدي أو مع قريني)
3) كم من شخص يقيم معك في المنزل؟ (اجب بصفر إذ أجبت ب "لا" على السؤالين الأول والثاني)
4) كم تتعهد من غرفة بالتنظيف في المنزل الذي تقيم فيه؟ (باحتساب المطبخ، غرفة النوم، المستودع، القبو، غرفة الاستحمام،
0. أنا لا أقوم ابدا بالتنظيف
1. من 1 إلى 6 غرف
2. من 7 إلى 10 غرف
3. أكثر من 10 غرف
5) على كم من طابق تتوزع تلك الغرف؟ (اجب بصفر إذ أجبت ب "لا" على السؤالين الأول والثاني)
6) هل تحضر اطعمتك الساخنة أو تشارك في تحضيرها؟
0. لا بتاتا
1. أحيانا (مرة أو مرتان في الأسبوع)
2. غالب الوقت (ثلاث أو أربعة مرات في الأسبوع).
3. دائما (أكثر من خمس مرات في الأسبوع).
7) كم عدد درجات السلم التي تصعدها في اليوم؟ (بحساب العشرات)
0. لا أصعد السلالم بتاتا
1. من 1 إلى5.
2. من 6 إلى 10
3. أكثر من 10
8) عند خروجك من المنزل ماهي وسائل النقل التي تستعملها؟
0. لا أخرج بتاتا من المنزل
1. السيارة
2. وسائل النقل العمومية (الحافلة، تاكسي، سيارة الأجرة...)
3. الدراجة الهوائية أو النارية
4. المشي
9) كم من مرة تخرج للتسوق في الأسبوع؟
0. أقل من مرة.
1. مرة فقط .
2. من 2 إلى 4.
3. كل يوم تقريبا
10) عند التسوق ما هي وسائل النقل التي تستعملها؟
0. لا اخرج بتاتا للتسوق
1. السيارة
2. وسائل النقل العمومية (الحافلة، تاكسي، سيارة الأجرة..).
3. الدراجة الهوائية أو النارية.
4. المشي.

) IIIالأنشطة الرياضية
هل تمارس الرياضة؟ نعم □ لا □

لرياضة الأولى
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

الرياضة الثانية
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

الرياضة الثالثة
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

الرياضة الرابعة
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

III) الأنشطة الترفيهية
هل تمارس أنشطة ترفيهية؟ نعم □ لا □

النشاط الأول
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

النشاط الثاني
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

النشاط الثالث
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....

النشاط الرابع
الاسم.....
عدد الساعات في الأسبوع.....
عدد الأشهر في السنة.....
درجة الحدة.....