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

Jihene Bergaoui1, Imed Latiri1,2, Helmi Ben Saad1,3

1 : Reasearch laboratory “Heart failure, LR12SP09”, Hospital Farhat HACHED, Sousse, Tunisia.
2 : Université de Sousse, Faculté de Médecine de Sousse, Laboratoire de Physiologie. Tunisie.
3 : Université de Sousse, Hôpital Farhat HACHED, Service de Physiologie et Explorations Fonctionnelles. Sousse, Tunisie.

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.

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

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
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 Advantage, 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\textsubscript{1}), forced-vital-capacity (FVC), and FEV\textsubscript{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\textsubscript{1}, FVC, and FEV\textsubscript{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\textsubscript{1}, FVC and FEV\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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, and HS data; 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.

**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.**

| Criteria | Cases | Controls |
|----------|-------|---------|
| **CHB diagnosis** | Viral activity assessed through qDNA-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 | |
| **Inclusion criteria** | Age: 30 to 50 years CHB diagnosed with a surface antigen persisting for at least 6 months before inclusion in the study AgHBc positive or negative with 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 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) | Study duration (months) | City (Country) | Main aims | Study design | Sample (M/F) | Populations | Characteristics of patients with CHB | Main results |
|------------------|-------------------------|----------------|-----------|--------------|--------------|-------------|-----------------------------------|--------------|
| Alameri (20)     | .12                      | Riyad (Saudi Arabia) | 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. | Prospective study | 250 (150/100) | 4 groups | Ag HBs+ ALT: normal or increased. Bilirubin, albumin, INR: normal. CBC: normal. Abdominal echography: normal. No PH or cirrhosis. | 6MWT: 6MWD (m), HR (bpm), oxy-sat (%), dyspnoea (Borg scale) |
| Galant (21)      | .5                       | Porto Alegre (Brazil) | To assess the correlation between VO$_{2peak}$ and respiratory muscle strength and QOL in patients with hepatic cirrhosis. | Cross-sectional study | 26 (14/12) | 3 groups (cirrhosis) | Age: 18-80*, 38±12* Height: NR Weight: NR BMI: 33.3±20.6* | VO$_{2peak}$ (mL/min/kg), Respiratory muscle strength: MIP/MEP (cmH$_2$O) |
| Galant (2)       | .5                       | Porto Alegre (Brazil) | To compare the muscle strength, exercise capacity and QOL data of 3 groups of patients with cirrhosis. | Cross-sectional study | 86 (64/22) | 3 groups (cirrhosis) | Age: 18-80*, 38±12* Height: NR Weight: NR BMI: 33.3±20.6* | VO$_{2peak}$ (mL/min/kg), Respiratory muscle strength: MIP/MEP (cmH$_2$O) |
| Faustini Pereira (3) | .3                      | Porto Alegre (Brazil) | To evaluate the relationship between the 6MWD, MIP, VO$_{2peak}$ and the survival rate of patients with cirrhosis. | Prospective study | 86 (66/20) | 3 groups (cirrhosis) | Age: 18-80*, 38±12* Height: NR Weight: NR BMI: 33.3±20.6* | VO$_{2peak}$ (mL/min/kg), Survival rate |
### Deficiency
- MIP: 73±22
- MEP: 79±29

### Incapacity
- 6MWD: GA: 421±47, GB: 390±53, GC: 357±72
- MIP: 82±14, GB: 72±15, GC: 66±11
- MEP: 79±29, GB: 83±12, GC: 65±11

### Social disadvantage
- SF-1 = 47±26, SF-2=65±22, SF-3=61±30, SF-4=52±18, SF-5=63±26, SF-6=71±25, SF-7=52±15, SF-8=68±10

### Conclusion
- There is a correlation between VO\textsubscript{2peak} and MIP.
- Patients have poor QOL.
- Compared to patients with cirrhosis post-CHB, those with cirrhosis post-CHB have better respiratory muscle strength, better exercise capacity, and better QOL.

### Other results
- VO\textsubscript{2peak} correlated with:
  - Age (r=-0.482)
  - Height (r=0.281)
  - Dyspnoea (r=-0.518)
  - Haemoglobin (r=0.373)
  - Albumin (r=0.311)

- 6MWD correlated with:
  - VO\textsubscript{2peak} (r=0.64)
  - MELD (r=0.56)

- Mortality
- 6MWD, MIP, VO\textsubscript{2peak}: predictors of mortality in patients with cirrhosis.

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**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. **G**: group. **GGT**: gamma-glutamyltranspeptidase. **HR**: heart-rate. **INR**: international-normalized-ratio. **M**: male. **MELD**: disease-severity-score. **MIP**: maximal-expiratory-pressure. **MEP**: maximal-inspiratory-pressure. **NA**: non-applied. **Oxy-sat**: oxygen saturation. **PH**: portal-hypertension. **QOL**: quality-of-life. **r**: coefficient of correlation. **6MWD**: 6-min-walk-distance. **6MWT**: 6-min-walk-test.

Date were expressed: Minimum-maximum; Mean.
The sample size was estimated using this formula (35): N = \left(1 + \frac{1}{r^2} \right) \left( Z_{\alpha/2} + Z_{1-\beta} \right)^2 s^2 / d^2.

- “Z_{\alpha/2}” is the normal deviate at a level of significance = 1.96 (5% level of significance);
- “Z_{1-\beta}” is the normal deviate at 1-\beta% power with \beta% 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\( \cdot \)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\( \cdot \)m\(^2\)), normal weight (BMI: 18.5-24.0 kg\( \cdot \)m\(^2\)), overweight (BMI: 25.0-29.9 kg\( \cdot \)m\(^2\)), and obesity (BMI ≥30 kg\( \cdot \)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 |
|---------------|-----------------------------|--------------------------------|-------------------------------------------------------------------------------------|-----|
|               | Haemoglobin                 | M: 14-17 g/dL; F: 12-16 g/dL   | Anaemia: haemoglobin < 12 (F) or < 14 (M) Polycythaemia: haemoglobin > 17           |     |
|               | Erythrocytes                | 4.2-5.9 $10^9$/mm$^3$         | Low: erythrocytes < 420000                                                          |     |
|               | Leucocytes                  | 4.5-11 $10^9$/mm$^3$          | Leukopenia: leucocytes < 4500 Leucocytosis: leucocytes > 11000                       |     |
|               | Neutrophils                 | 2.6-8.5 $10^9$/mm$^3$         | High: neutrophils > 8500                                                             |     |
|               | Eosinophils                 | 0-0.55 $10^9$/mm$^3$          | High: eosinophils > 550                                                              |     |
|               | Basophils                   | 0-0.22 $10^9$/mm$^3$          | Basocythemia: basophils > 220                                                       |     |
| EDTA          | Lymphocytes                 | 0.77-4.5 $10^9$/mm$^3$        | Lymphopenia: lymphocytes < 770                                                       |     |
|               | Monocytes                   | 0.14-1.3 $10^9$/mm$^3$        | Monocytosis: monocytes > 1300                                                        |     |
|               | Thrombocytes                | 150-350 $10^9$/mm$^3$         | Thrombocytopenia: thrombocytes < 150000 Thrombocytosis: thrombocytes > 350000       |     |
|               | ESR- 1st hour               | M: 0-15 mm; F: 0-20 mm        | Biological inflammatory syndrome: ESR > 15 (M) or > 20 (F)                           |     |
| Citrate       | Prothrombin-level           | 70-100%                       | Low: prothrombin-level < 70%                                                        |     |

**ETDA:** 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                                                                   |     |
|               |                | Creatinine                  | 7-13 mg/L                      | High: creatinine > 14                                                               |     |
| Lithium heparin | Liver function | AST                          | 0-35 U/L                       | Cytolysis: AST > 35                                                                |     |
|               |                | Total-bilirubin              | 0.3-1.2 mg/dL                  | High: bilirubin > 1.2                                                              |     |
|               |                | Conjugated-bilirubin         | 0-0.3 mg/dL                    | High: bilirubin > 0.3                                                               |     |
|               |                | GGT                          | 8-78 U/L                       | High: GGT > 78                                                                     |     |
|               |                | Albumin                     | 35-54 g/L                      | Low: albumin < 35                                                                 |     |
| Dry tube      | Lipid panel     | TC                           | 3.88-5.15 mmol/L               | High: TC > 5.15                                                                    |     |
|               |                | TG                           | < 2.82 mmol/L                  | High: TG > 2.82                                                                    |     |
|               |                | HDL-C                        | ≥ 1.04 mmol/L                  | Low: HDL-C < 1.04                                                                  |     |
|               |                | LDL-C (=TC-HDL-C - TG/5)     | ≤ 3.36 mmol/L                  | High: LDL-C > 3.36                                                                 |     |
| Lithium heparin | Others          | UA                           | 0.15-0.47 mmol/L               | High: UA > 0.47                                                                    |     |
|               |                | CRP                          | < 5 mg/L                       | Biological inflammatory syndrome: CRP > 12                                           |     |
|               |                | CPK                          | 30-170 U/L                     | Myolysis: CPK > 17                                                                |     |
| Fluoride      | Fasting-glycaemia |                 | 3.9-5.8 mmol/L                 | High: glycaemia > 5.8                                                               |     |

**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 ($t_{rest}$) and immediately at the end ($t_{end}$) of the 6MWT. The maximal predicted heart-rate will be calculated \[ = 208 \times 0.7 \times \text{Age} \] (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 (ΔOxy-sat = Oxy-sat$_{end}$ - Oxy-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-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 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.

REFERENCES

1. Dienstag JL. Hepatitis B as an immune complex disease. Semin Liver Dis.
1981;1(1):45-57.
2. Galant LH, Forgiarini Junior LA, Dias AS, Marroni CA. Functional status,
respiratory muscle strength, and quality of life in patients with cirrhosis.
Rev Bras Fisioter. 2012;16(1):30-4.
3. Faustini Pereira JL, Galant LH, Rossi D, Telles da Rosa LH, Garcia E, de
Mello Brandao AB, et al. Functional capacity, respiratory muscle strength,
and oxygen consumption predict mortality in patients with cirrhosis. Can J
Gastroenterol Hepatol. 2016;2016:6940374.
4. Maruyama S, Koda M, Murawaki Y. Myocardial perfusion defects in
patients with chronic hepatitis B infection. J Gastroenterol Hepatol.
2014;29(4):794-9.
5. Sehonou J, Kpossou AR, Amanda TO, Sokpon CNM, Vignon RK, Vigan J.
Hepatitis B and renal failure: prevalence and associated factors in National
university hospital center of Cotonou. Pan Afr Med J. 2018;31(121):121.
6. Hafeez M, Sarfraz T, Khan RG, Rafe A, Rasool G, Ahmed KN. Hepatitis
B leading to megaloblastic anaemia and catastrophic peripheral
thrombocytopenia. J Coll Physicians Surg Pak. 2016;26(12):992-4.
7. Hong YS, Chang Y, Ryu S, Caiinzos-Achirica M, Kwon MJ, Zhang Y, et al.
Hepatitis B and C virus infection and diabetes mellitus: A cohort study. Sci
Rep. 2017;7(1):4606.
8. Liang TJ. Hepatitis B: the virus and disease. Hepatology. 2008;49(5
Suppl):S13-21.
9. International classification of functioning, disability and health (ICF).
Available from http://www.who.int/classifications/icf/en/ (Last visit: July
25th 2021)
10. Goh LY, Card T, Fogarty AW, McKeever TM. The association of exposure
to hepatitis B and C viruses with lung function and respiratory disease:
a population based study from the NHANES III database. Respir Med.
2014;108(12):1733-40.
11. Teuber G, Teupe C, Dietrich CF, Caspary WF, Buhl R, Zeuzem S.
Pulmonary dysfunction in non-cirrhotic patients with chronic viral hepatitis.
Eur J Intern Med. 2002;13(5):311-8.
12. Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip
dynamometry. Curr Opin Clin Nutr Metab Care. 2015;18(5):465-70.
13. Beseler MR, Rubico C, Duarte E, Hervas D, Guevara MC, Giner-Pascual
M, et al. Clinical effectiveness of grip strength in predicting ambulation of
elderly inpatients. Clin Interv Aging. 2014;9:1873-7.
14. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Jr.,
Orlandini A, et al. Prognostic value of grip strength: findings from the
Prospective Urban Rural Epidemiology (PURE) study. Lancet.
2015;386(9990):266-73.
15. Sharma P, Rauf A, Matin A, Agarwal R, Tyagi P, Arora A. Handgrip strength
as an important bed side tool to assess malnutrition in patient with liver
disease. J Clin Exp Hepatol. 2017;7(1):16-22.
16. Hiraoka A, Tamura R, Oka M, Izumoto H, Ueki H, Tsuruta M, et al.
Prediction of risk of falls based on handgrip strength in chronic liver
disease patients living independently. Hepatol Res. 2019;49(7):823-9.
17. Itoh S, Shirabe K, Yoshizumi T, Takeishi K, Harimoto N, Ikegami T, et al. Skeletal muscle mass assessed by computed tomography correlates to muscle strength and physical performance at a liver-related hospital experience. Hepatol Res. 2016;46(4):292-7.

18. Nagamatsu S, Kawaguchi T, Hirota K, Koya S, Tomita M, Hashida R, et al. Slow walking speed overlapped with low handgrip strength in chronic liver disease patients with hepatocellular carcinoma. Hepatol Res. 2019;49(12):1427-40.

19. Lee K. Relationship between handgrip strength and nonalcoholic fatty liver disease: Nationwide surveys. Metab Syndr Relat Disord. 2018;16(9):497-503.

20. Alamri HF, Sanai FM, Al Dukhayil M, Azzam NA, Al-Swat KA, Hersi AS, et al. Six minute walk test to assess functional capacity in chronic liver disease patients. World J Gastroenterol. 2007;13(29):3996-4001.

21. Galant LH, Forgiani LA, Jr., Dias AS. The aerobic capacity and muscle strength are correlated in candidates for liver transplantation. Arch Gastroenterol. 2011;48(1):86-8.

22. Ben Saad H, Prefaut C, Tabka Z, Mitr AH, Chemit M, Hassaoune R, et al. 6-minute walk distance in healthy North Africans older than 40 years: influence of parity. Respir Med. 2009;103(1):74-84.

23. Cramm JM, Adams SA, Walters BH, Tsiachristas A, Bal R, Huijsman R, et al. The role of disease management programs in the health behavior of chronically ill patients. Patient Educ Couns. 2014;95(1):137-42.

24. Karacaer Z, Cakir B, Erdem H, Ugurlu K, Durmus G, Ince NK, et al. Quality of life and related factors among chronic hepatitis B-infected patients: a multi-center study. Turkey. Health Qual Life Outcomes. 2016;14(1):153.

25. Bondini S, Kallman J, Dan A, Younoszai Z, Ramsey L, Nader F, et al. Health-related quality of life in patients with chronic hepatitis B. Liver Int. 2007;27(6):1119-25.

26. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999;45(2):295-300.

27. Yi YH, Kim YJ, Lee SY, Cho BH, Cho YH, Lee JG. Health behaviors of Korean adults with hepatitis B: Findings of the 2016 Korean national health and nutrition examination survey. World J Gastroenterol. 2018;24(28):3163-70.

28. Younossi ZM, Stepanova M, Younossi I, Racila A. Development and validation of a hepatitis B-specific health-related quality-of-life instrument: CLDQ-HBV. J Viral Hepat. 2021;28(3):484-492.

29. Newsom JT, Huguet N, McCarthy MJ, Ramage-Morin P, Kaplan MS, Bernier J, et al. Health behavior change following chronic illness in middle and later life. J Gerontol B Psychol Sci Soc Sci. 2012;67(3):279-88.

30. Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agusti A, Criner GJ, et al. An official American thoracic society/European respiratory society statement: research questions in COPD. Eur Respir J. 2015;45(4):879-905.

31. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American college of sports medicine and the American heart association. Med Sci Sports Exerc. 2007;39(8):1423-34.

32. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. Med Sci Sports Exerc. 1991;23(8):974-9.

33. Berk PD, Popper H. Fulminant hepatic failure. Am J Gastroenterol. 1978;69(3 Pt 2):349-400.

34. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, et al. An official systematic review of the European respiratory society/ American thoracic society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1447-78.

35. Serhier Z, Bendahhou K, Ben Abdelaziz A, Bennani MO. Methodological sheet n°1: How to calculate the size of a sample for an observational study? Tunis Med. 2020 Jan;98(1):1-7.

36. Abdelghani A, Ben Saad H, Ben Hassen I, Ghannouchi I, Ghraihi H, Bougniza I, et al. Evaluation of the deficiency and the submaximal exercise capacity in obstructive sleep apnoea patients. Rev Mal Respir. 2010;27(3):266-74.

37. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet. 2006;367(9508):404-11.

38. Haeckel R. Simplified determinations of the “true” creatinine concentration in serum and urine. J Clin Chem Clin Biochem. 1980;18(7):385-94.

39. Colombet I, Pouchot J, Kroz V, Hannas X, Capron L, Durieux P, et al. Agreement between erythrocyte sedimentation rate and C-reactive protein in hospital practice. Am J Med. 2010;123(9):863 e7-13.

40. Blood tests: normal values. MSD Manual. Professional version. Available from: https://www.msdmanuals.com/professional/resources/normal-laboratory-values/blood-tests-normal-values (Last visit: July 25th 2021).

41. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.

42. Cadenas-Sanchez C, Sanchez-Delgado G, Martinez-Tellez B, Mora-Gonzalez J, Lof M, Espana-Romero V, et al. Reliability and validity of different models of TKK hand dynamometers. Am J Occup Ther. 2016;70(4):7004300010.

43. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-58.

44. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

45. Kammoun R, Ben Saad H. From deficiency to handicap in the
