The effect of mHealth-based exercise on Insulin Sensitivity for patients with Hepatocellular carcinoma and insulin resistance (mISH): protocol of a randomized controlled trial.

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Research Article

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Abstract

Background

The importance of insulin resistance is gaining increasing attention as it plays an important role in carcinogenesis in hepatocellular carcinoma (HCC). Although exercise is the most important intervention for lowering insulin resistance, it is not easy for HCC patients to maintain high compliance and do appropriate exercise. Mobile health (mHealth) with wearable devices, can be the solution to carry out an adjusted and supervised exercise that can improve insulin resistance in patients with HCC. We developed an HCC-specific application equipped with patient-centered exercise. In this paper, we present a randomized controlled trial protocol that compares the exercise group with the usual follow-up care group to determine if mHealth-based exercise has the effect of improving insulin sensitivity in HCC patients with insulin resistance after anticancer treatment.

Methods

An assessor-blind, randomized controlled trial (RCT) will be conducted for 80 participants who have received curative treatment and are in a complete response at the time of screening, with or without treatment-naive or recurrent HCC. They will be randomly assigned (1:1) to one of two groups: an intervention group ($n = 40$) and a control group ($n = 40$). The intervention group will carry out mHealth-based exercise for 6 months from baseline, whereas the control group will receive the usual follow-up care for the first 3 months and mHealth-based exercise for the next 3 months. Both groups will be assessed at baseline, 3 months and 6 months from baseline. The primary outcome is the improvement of insulin sensitivity at 3 months. The secondary outcomes include improvement of insulin sensitivity at 6 months, body composition, physical fitness level, physical activity, quality of life and adverse events at 3 and 6 months.

Discussion

This study is the first RCT to investigate the effect of mHealth-based home exercise with a wrist-wearable device on insulin sensitivity, physical fitness, and quality of life (QoL) for HCC patients with insulin resistance. The result of this RCT will confirm not only safety and functional improvement but also biological effect when exercising using mHealth in HCC patients.

Trial registration:

ClinicalTrials.gov, NCT04649671. Registered 2 December 2020, https://clinicaltrials.gov/ct2/show/NCT04649671

Background

The growing interest in the association between exercise and cancer has led to an increase in research on this topic. It is proven that exercise has a preventive effect in seven types of cancer (colon, breast, endometrial, kidney, bladder, esophagus and stomach) and improves survival in three types of cancer (breast, colon and prostate) [1, 2]. In addition to the preventive effect of exercise, there is sufficient evidence that exercise improves common cancer-related health outcomes in a variety of cancers, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life [3]. However, little is known about the role of exercise for patients with hepatocellular carcinoma (HCC), which has the 4th highest mortality rate of all cancers [4].

Viral hepatitis in the East and alcohol or fatty liver/metabolic disease in the West are major risk factors for HCC. Fatty liver and metabolic diseases are changing as a major risk factor in the current westernized world and the risk posed by these is expected to increase in the future [5]. One of the main mechanisms by which fatty liver and metabolic diseases cause HCC is insulin resistance, and several studies show that there is a link between the two in patients with or without viral hepatitis [6]. Insulin resistance promotes fatty degeneration of the liver and inflammatory response of adipocytes, which leads to non-alcoholic fatty liver disease and further cirrhosis and liver cancer. Therefore, it is thought that reducing insulin resistance can improve liver function and reduce the incidence of liver cancer. The most basic and essential treatment for insulin resistance is exercise [7]. In fact, one animal study has shown rats that engage in regular physical activity have a lower primary occurrence of HCC [8]. Exercise is expected to have a positive effect on patients with HCC, but patients and doctors consider hepatic decompensation to be a risk when exercising [9]. Only a few studies have reported the positive effects of in-hospital exercise for HCC patients [10–12]. Longer-term exercise interventions are necessary, especially for cancer patients, but it is not practical for all interventions to be carried in hospitals. Digital health, especially mobile health (mHealth) with wearable devices, is a promising solution that can allow patients with HCC to carry out adjusted and supervised exercise without the risk of hepatic decompensation. The usefulness and effectiveness of mHealth has been reported for several cancers, such as breast [13] and prostate [14] cancer. Our previous study presented the efficacy and safety of the mHealth application and wearable devices, and their physical performance for patients with HCC [15]. Our surveillance system comprised of a wearable Internet of Things (IoT) device and an HCC-specific application that showed no complications or biochemical deterioration, with an improvement in physical performance during the 12-week intervention. However, the biological improvement of insulin resistance was not confirmed, there was no control group for comparison, intervention period was relatively short and the exercise intensity was manually readjusted once. Hence, we modified the HCC-specific application with monitored patient-centered exercises and we planned a randomized controlled trial (RCT) using this application. The intervention group should be carried out with mHealth-based exercises for 6 months and the control group should receive usual follow-up care for the first 3 months and mHealth-based exercise for the following 3 months. This exercise intervention is conducted for longer than that in usual intervention studies and patient compliance can be determined with the wearable device. In addition, the exercise

intensity conversion algorithm based on the rating of perceived exertion (RPE) is applied for aerobic exercises in this application.

It is assumed that the insulin sensitivity, physical fitness, and quality of life (QoL) of HCC patients with insulin resistance can be improved by using the mobile application and an exercise program specialized for HCC patients after anticancer therapy. This paper presents an assessor-blinded 1:1 randomized controlled trial protocol comparing the exercise group with a usual follow-up care group to determine the effect of the **m**Health-based exercise on **I**nsulin **S**ensitivity for patients with **H**CC and insulin resistance (mISH) after anticancer therapy.

Methods/design

Study design

This protocol is an assessor-blinded RCT that compares usual follow-up care with mISH to help patients improve insulin sensitivity, physical fitness and QoL from baseline to 12 weeks. Participants will be collected in one academic hospital (Samsung Medical Center, South Korea).

Study procedure

Figure 1 outlines the flowchart of the RCT and Table 1 indicates the summary of baseline screening, enrolment, and assessment during study visits. The patients with treatment-naïve and recurrent HCC who have received treatment and achieved complete response at the time of screening will be screened about general condition, alcohol intake history, liver function, medical history and drug history. A written consent including collection and use of participant data and biological specimens will be obtained from the participant by physician investigator. Homeostatic model assessment for insulin resistance (HOMA-IR) will be assessed. Among screened participants, only patients with insulin resistance (HOMA-IR $\geq$ 2.2) will be enrolled in outpatient clinic. After enrollment, they need to be randomized based on 1:1 allocation to two groups: the intervention group should carry out mISH for 6 months, and the control group should receive the usual care for the first 3 months and mISH for the next 3 months. Participants should continue to take medications for other conditions as normal. In addition, the individual's additional physical activity is not restricted. In both groups, assessments for the primary outcome will be performed after 3 months from baseline, and assessments for the secondary outcomes will be performed after 6 months from baseline.

Allocation and randomization

Participants will be randomly assigned to the intervention group (n = 40), receiving 12 weeks of mISH or to the control group (n = 40), not receiving mISH, in a 1:1 ratio. Randomization will be carried out by the researcher who do not perform assessments and will be computer generated and overseen by researchers. The baseline assessments will be performed after allocation and randomization.

Participants

A total of 80 participants need to be included in the study.

Inclusion criteria

Adults aged 20–70

Early-stage HCC, defined by modified International Union Against Cancer (UICC) stage 1 or 2

Participants who have received curative treatment and are in a complete response at the time of screening, with or without treatment-naive or recurrent HCC

Insulin resistance (Homeostatic model assessment for insulin resistance (HOMA-IR) ≥ 2.2)

Eastern Cooperative Oncology Group (ECOG) performance status of 0–2

Exclusion criteria

Participants who disagree with the guidelines of the study

Decreased liver function (Child Pugh class B or C)

Bad general condition (Eastern cooperative oncology group (ECOG) > 2)

Excessive drinkers (more than 20 g of alcohol intake per day)

History of decompensated cirrhosis

Inability to exercise due to severe heart and lung diseases (heart failure, ischemic heart disease, 3rd degree atrioventricular block, chronic obstructive pulmonary disease, severe high blood pressure (> 200/100 mmHg))

Inability to exercise due to serious mental illness

Use of insulin sensitizers (sulfonylurea, biguanide, thiazolidinediones, Glucagon like peptide-1 agonist, Dipeptidyl peptidase-4 inhibitor) or those who take insulin

Uncontrolled diabetes (hemoglobin A1c > 10%)

Criteria for discontinuing interventions

If participants meet the exclusion criteria

Tumor recurrence

Participants request

Intervention

A wearable IoT device and a mobile application-equipped exercise program specialized for HCC will be provided. The intervention group will use mISH for 6 months, whereas the control group will receive usual follow-up care for the first 3 months and mISH for the next 3 months. Personal exercise will be permitted during the trial.

Intervention group

The mobile application, exercise program, and wearable IoT device comprise one intervention. The application uses data input from a wearable IoT device, Dofit (NF-B20, Medi Plus Solution, Seoul, South Korea). Dofit measures heart rate and physical activity (step counts and calories burned) when worn on the wrist. The application provides information on exercise management (aerobic and resistance exercises), activity tracking, diet management, medication management, and health consultation. Screenshots for each domain of the application are shown in Fig. 2. Each domain consists of the followings; main page, menu tab, exercise management, activity tracking, diet management, medication management, and health consultation. Researchers will monitor and feedback on exercise performance.

Exercise management

The application offers aerobic and resistance exercises. For aerobic exercise, when the start button is pressed, the exercise time is recorded and the heart rate during exercise is measured and displayed in real-time. The intensity of aerobic exercises is prescribed at the target heart rate (THR) according to American College of Sports Medicine (ACSM) guidelines [16].

If a participant is enrolled less than 16 weeks after surgery or radiofrequency ablation (RFA), the intensity of aerobic exercise and resistance exercise is designed to increase step by step from week 1 to week 15. From week 1 to week 15, the intensity of aerobic exercise is set to increase from 58–68% of maximum heart rate and the intensity of resistance exercise is also set to increase [see Additional file 1]. From the week 16 after surgery of RFA, general exercise management begins, and exercise intensity is adjusted according to the RPE.

If a participant is enrolled 16 weeks after surgery, baseline 6 minute walk test (6 MWT) is used to control the initial intensity of exercise. If the baseline 6 MWT result is better than the average level for the same age and sex, the THR for initial aerobic exercise is 72% of the maximum heart rate, and general exercise management begins immediately. If the baseline 6 MWT result is less than the average level for the same age and sex, after maintaining the THR at 68% of maximum heart rate for one month, general exercise management begins. The average value of 6 MWT according to age and sex will be calculated using the following formula [17].

Men (m) = (7.57 x height cm)-(5.02 x age)-(1.76 x weight kg)-309

Women (m) = (2.11 x height cm)-(2.29 x weight kg)-(5.78 x age) + 667

In general exercise management, the THR of the next exercise is determined based on the RPE after the end of the previous exercise. If the participant records “very hard” even once, the exercise intensity is decreased, and if the participant records “very light” or “moderate” twice or more, the exercise intensity is increased. Exercise intensity is estimated by a RPE of 13 (a bit hard) – 15 (hard). In patients with hypertension, the THR is set lower. Participants can check their smart band to monitor their heart rate during aerobic exercise. Notifications are sent to them to inform them if the THR is achieved. This is useful to evaluate the participants’ compliance and to monitor if the participants exercise properly by looking for an increase in heart rate.

When general exercise management is started, the intensity of resistance exercise is also adjusted based on RPE and participants need to follow the video clips of exercises. Video exercise starts with a warm-up, resistance exercises using an elastic band, and finishes with stretching (cool-down).

Healthcare professionals and researchers will access exercise logs through a monitoring platform and will provide weekly guidance and positive reinforcement.

Activity tracking

Participants can review daily step counts using Dofit. The application displays daily step counts of general walking, fast walking, and running. It calculates and displays the calories burned from physical activity during the day.

Diet management

Based on the user’s body mass index, the necessary calories and customized daily diet guides specialized for HCC are provided. When participants enter the type and amount of food they eat, the application displays if the amount of carbohydrates and protein consumed is over or under the expert's recommendation. Participants can also check if the balance of the food groups they eat is adequate.

Medication management

When medications are registered on the application, an alarm for timely medication is provided on the main screen.

Health consultation

The participants are informed of precautions necessary and complications that may occur depending on their cancer treatment process, and the app warns of symptoms that require a hospital visit. When participants have questions about their health or exercise, they are able to consult with physical therapists and physicians.

Control group

All participants will receive the same brochure previously provided to HCC patients after anticancer therapy (radiofrequency ablation, hepatectomy, transarterial chemoembolization or radiotherapy). It lists guidelines for healthy living post anticancer therapy and diet specifications such as eating a high-protein

diet, eating snacks in the late evening, and avoiding very spicy or salty foods and herbal medicines. An acceptable level of exercise intensity is also recommended in the brochure.

Measurements

Data from electronic medical record will be used. All participants need to answer a self-administered questionnaire that includes a history of hypertension, diabetes, stroke, use of medications, alcohol, and smoking. Height and waist will be measured to the nearest half centimeter. Weight will be measured to the nearest half kilogram. Blood pressure will be measured after at least 10 minutes resting. The weight and waist will be measured at each assessment point.

Serum blood tests at baseline include the following: platelet count, hemoglobin A1c, fasting blood glucose, insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time-international normalized ratio (PT INR), albumin, total bilirubin, alpha-fetoprotein, proteins induced by vitamin K absence of antagonist-II (PIVKA –II), high density lipoprotein cholesterol (HDL), triglyceride, and low density lipoprotein cholesterol (LDL). Among the above items, fasting glucose, insulin, hemoglobin A1c and lipid profile will be measured at each assessment point.

Assessments

Assessments, such as blood test (fasting glucose, insulin, hemoglobin A1c and lipid profile), physical activity and QoL questionnaires, and physical fitness assessments will be carried out at baseline, 3 and 6 months after baseline. A nutritional assessment will be done to determine if there are any nutritional differences between the two groups.

Primary outcome

The primary outcome is responder rates of improvement of insulin resistance at 12 weeks of mISH. Insulin resistance is estimated by calculating HOMA-IR, which uses the computer-based solution of the model provided by the Diabetes Trials Unit, Oxford Center for Diabetes, Endocrinology, and Metabolism (http://www.dtu.ox.ac.uk/homa). Responders are patients who fulfilled improvements of HOMA-IR value less than 2.2.

Secondary outcome

The secondary outcomes are the responder rates of insulin resistance at 24 weeks of mISH, improvement of hemoglobin A1c, lipid profile, body composition, physical fitness, and patient-reported outcome such as physical activity level, QoL, and adverse events. Fasting glucose, insulin, hemoglobin A1c and lipid profile will be measured at baseline, 3 and 6 months after baseline. Data for the body composition analyses is collected using a bioelectric impedance device, Inbody 720 (Biospace). Muscle mass and body fat percentage will be recorded and body mass index (BMI) will be calculated as body weight/height^2 (kg/m^2).

Physical fitness is measured by the grip strength test, the 30 s chair stand test, and the 6 MWT. A digital hand-held dynamometer (microFET® HandGRIP; Hoggan Health, Salt Lake City, UT), is used to assess the upper extremity muscle strength. Seated participants hold the dynamometer in their arm with shoulder adducted, elbow flexed to 90 degrees, and forearm and wrists resting in a neutral position. After 3 s, the maximum power is measured. The experiment is performed on the other side in the similar way. We use an average of the 3 grip strength tests. A 30 s chair stand test is performed to evaluate the strength of the lower extremities. Participants are made to sit straight in a chair without the support of the backrest and with both arms folded across the chest. For 30 s, they complete stand-up and sit-down motions as quickly as possible and the number of motions is counted. To estimate the level of cardiopulmonary endurance, the 6 MWT is conducted. The total distance walked at maximal speed for 6 minute is recorded.

Physical activity levels are objectively measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) questionnaire. This questionnaire includes 9 questions on time spent on vigorous and moderate activities and time spent walking or sitting for the preceding 7 days. The total number of metabolic equivalents (METs) per week can be calculated using this questionnaire. The calculated physical activity is classified into 3 IPAQ-SF categories: inactive (< 600 METs), minimally active (≥ 600 to < 3000), and highly active (≥ 3000).

General health-related QoL is assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). The questionnaire includes 30 questions regarding global health status, functional scales and symptom scales. Higher scores on the general health status and functional scales indicate positive outcomes, while high symptom scales are considered negative. Adverse events are also reported using EORTC-QLQ-C30.

General nutritional status is assessed by the mini nutritional assessment (MNA). The MNA consists of 18 questions derived from four parameters of assessment: anthropometric, general, dietary, and subjective. The total score for the full MNA will fall between 0 and 30 points: 24 and higher indicates a well-nourished patient; 17 to 23.5 indicates a risk of malnutrition; lower than 17 indicates malnutrition.

Sample size calculation

The target number of participants was calculated using the nQuery 8.5 program with the guidance of biostatisticians of Samsung Medical Center. Assuming that the rate of improvement in HOMA-IR level in the intervention group is 30% and 5% in the control group, 36 participants per group are required to achieve 80% power and 5% significance level. Considering a 10% dropout rate, a final 40 participants need to be recruited for each group. This is an assessor-blinded randomized design study; hence, participants are randomly assigned to either the intervention group or the control group by a random number table. Block randomization with an allocation ratio of 1:1 is implemented.

Statistical analysis

The strategy for statistical analysis is developed under the supervision of a biostatistician at the Samsung Medical Center. Analyses will be performed using an intention-to-treat approach. Descriptive statistics will be used to present baseline characteristics of both groups. For the primary outcome, the proportion of participants with improved insulin sensitivity at 3 months after baseline in each group will be compared using the chi-square test. For the second outcome, the responder rates of improved insulin sensitivity at 6 months after baseline will be compared using the chi-square test. Changes in hemoglobin A1c, lipid profile, body composition, physical fitness level, physical activity, general health related quality of life and adverse events at 3 months after baseline will be compared by an unpaired t-test. The repeated measured analysis of variance analysis (RMANOVA) will be used to test whether there are differences in insulin sensitivity, physical activity, QoL, body composition and physical fitness between groups. If there is a significant difference, a post-hoc test should be performed to determine if there is a difference between groups at each point of time (3 months and 6 months after baseline) and changes over time within the group. All tests will use a 5% level of significance ($p < 0.05$).

Data management

All participant data will be collected and coded by research team members and will be stored and will be password protected in the secured platform accessible only principal investigators. Backup database will be updated regularly. The anonymized dataset will be available on request to the corresponding authors. No interim analysis will be performed prior to the end of the study.

Patient and public involvement

No patient involved.

Participant safety and withdrawal

The potential risk level reviewed by institutional review board and principal investigator is minimal. For prevention and management in adverse events, participants can call researchers at any time if they have any question or problems. If there are an intolerable muscle pain or injury, they will visit a hospital and will be examined their condition by principal investigator.

All participants are able to discontinue voluntarily the study at any time and they can be withdrawn in case of the significant disease non-related to study, and not following instruction of doctor in charge.

Ethics and dissemination

This study was approved by the institutional review board (IRB) of Samsung Medical Center (number: 2020-06-037). Current protocol version is 2.3 and approved on 27 October 2021. In the event of important protocol modifications, it will be reported to the IRB and approved after the consent of the physician investigator and co-researchers. The trial was prospectively registered on the ClnicalTrials.gov website (trial number: NCT04649671). The dissemination of research will occur through several pathways. The research results will be submitted for publication to peer-reviewed journals, both nationally and

internationally. The protocol adheres to the recommended standard protocol items: recommendations for interventional trials (SPIRIT) checklist [see Additional file 2].

Discussion

Studies are increasingly researching the association between cancer and exercise. Exercise can reduce incidence of various cancers and can increase survival in some cancers [1, 2]. Although few studies exist on the effects of exercise for patients with HCC when compared to those with other cancers, recently the focus on HCC has increased. A study reported that there was a reverse correlation between the degree of physical activity and the incidence of HCC [18]. The anti-tumor effects of exercise on HCC are primarily associated with weight loss, insulin resistance, and chronic inflammation [19]. Several studies investigated insulin resistance and hyperinsulinemia promotes oxidative stress and activity of insulin-like growth factor 1, a peptide that stimulates growth of liver cells and may play a role in hepatocarcinogenesis. The results suggest that lowering insulin resistance through interventions including exercise and calorie restriction may be a treatment option for HCC. Although there is both theoretical and experimental evidence on the effect of exercise on HCC patients, in actual clinical practice, due to concerns about hepatic decompensation, sufficient exercise is not conducted by HCC patients. This risk of HCC requires close monitoring of the patient's symptoms and exercise intensity with a detailed exercise regimen. For this reason, only a few studies have reported the positive effects of "in-hospital exercise" for patients with HCC [10–12].

New exercise system can be realized using mHealth as it is possible to adjust the intensity of exercise based on real-time feedback and in-application chat with experts, and to monitoring dangerous symptoms. Moreover, the mHealth-based exercise can be performed anywhere, at any moment. Previously, we have confirmed that the application and exercise program using Dofit are safe and effective [15]. This RCT will be upgraded to an application with an exercise intensity control algorithm. The intervention group will work out with mHealth for 6 months, the control group will receive usual care for the first 3 months and mHealth-based exercise for the next 3 months.

This study has several strengths; to the best of our knowledge, this is the first RCT to demonstrate the beneficial effect of mHealth-based exercise with wearable IoT device in HCC patients with insulin resistance. Second, this RCT investigates if there is a biological effect on insulin sensitivity, physical fitness, and QoL. Third, as participants are prescribed longer-term exercise interventions when compared to previous studies, this study can ensure adherence to long-term mHealth-based exercises.

One limitation of this study is that it is difficult to determine the generalizability to other HCC patients because only subjects with complete remission and preserved liver function participate in this study.

In conclusion, the results of this RCT can provide evidence for mHealth to be a safe way to enable exercising by patients with HCC.

Trial status

ClinicalTrials.gov Identifier: NCT04649671. First posted on December 2, 2020; last update posted on February 25, 2022. Actual study started on March 16, 2021 and estimated study completion date is October 31, 2023.

https://clinicaltrials.gov/ct2/show/NCT04649671

List Of Abbreviations

HCC: Hepatocellular carcinoma; mHealth: Mobile health; IoT: Internet of Things; RCT: Randomized controlled trial; RPE: Rating of perceived exertion; QoL: Quality of life; mISH: mHealth-based exercise on Insulin Sensitivity for patients with HCC and insulin resistance; HOMA-IR: Homeostatic model assessment for insulin resistance; UICC: International Union Against Cancer; THR: Target heart rate; ACSM: American College of Sports Medicine; RFA: Radiofrequency ablation; 6 MWT: 6 minute walk test; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT INR: Prothrombin time-international normalized ratio; PIVKA –II: Proteins induced by vitamin K absence of antagonist-II; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; BMI: Body mass index; IPAQ-SF: International Physical Activity Questionnaire-Short Form, METs: Metabolic equivalents; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; MNA: Mini nutritional assessment; RMANOVA: Repeated measured analysis of variance analysis; IRB: Institutional review board; SPIRIT: Standard protocol items: recommendations for interventional trials.

Declarations

Ethics approval and consent to participate

The study will be performed in accordance with the Declaration of Helsinki. This study protocol received ethical approval from the Institutional Review Board (Samsung Medical Center, 2020-06-037). All patients will sign the written informed consent to allow the use of their data for research purposes.

Consent for publication

Not applicable.

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Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DHS and JHO conceived the project idea and designed the study together with JHH and SMY. SMY and HJY drafted this manuscript and all the authors provide feedback on the drafts, and have read and approved the final manuscript.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

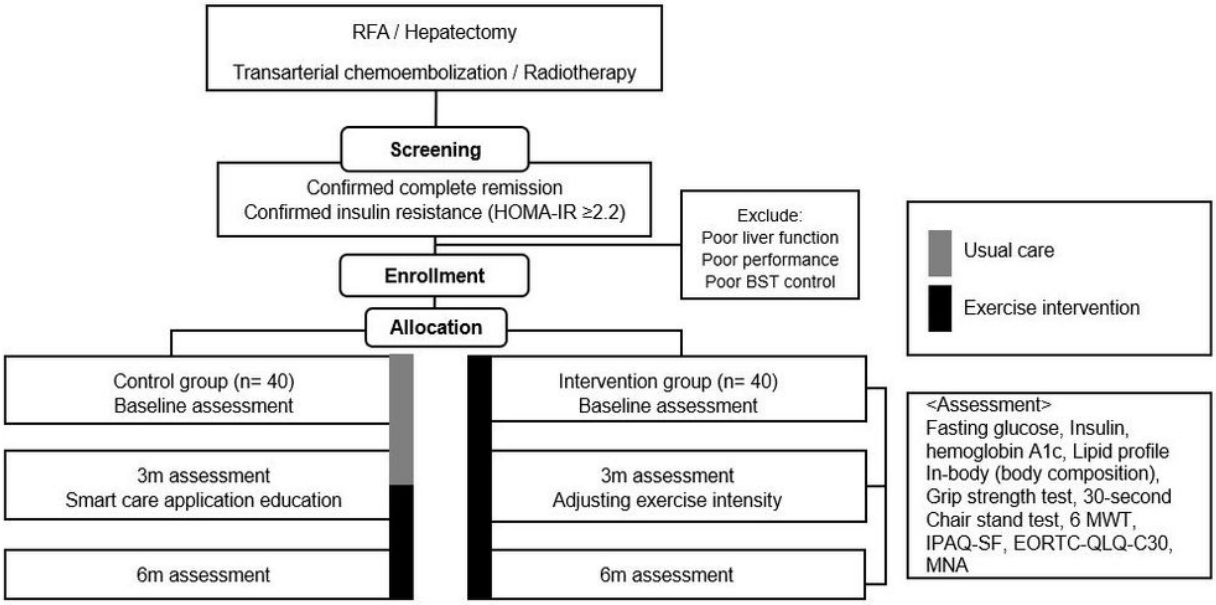

Figure 1

Participant flow through the randomized controlled trial. RFA, radiofrequency ablation; HOMA-IR, Homeostatic model assessment for insulin resistance; 6 MWT, 6 minute walk test; IPAQ-SF, Korean version international physical activity questionnaire-short form; EORTC-QOL-C30, European organization for research and treatment of cancer quality of life questionnaire C30; MNA, Mini nutritional assessment

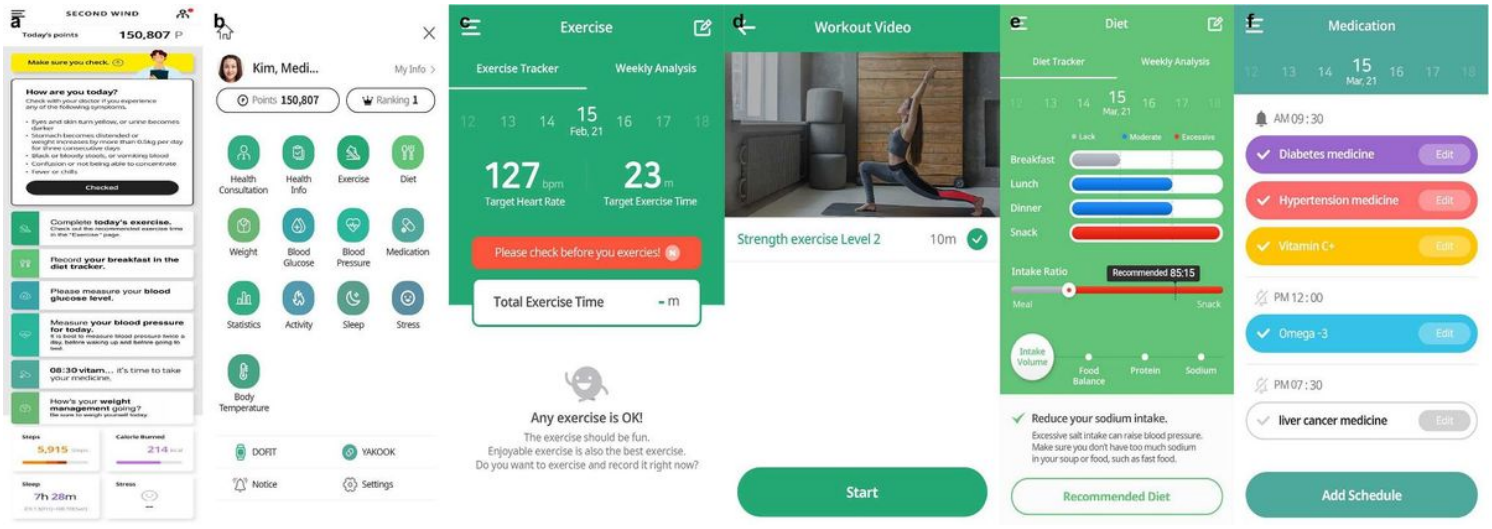

Figure 2

Application screenshots. Screenshots of the main page (a), menu tab (b), exercise management (aerobic exercise [c] and resistance exercise [d]), diet management (e), and medication management (f).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg
- Additionalfile1.docx
- Additionalfile2.doc