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Physical Activity, Energy, Nutrition and Understanding Laboratory Parameters in Chronic Kidney Disease (CKD) Patients - Pilot Findings Following an Educational Webinar *via* a Social Media Platform

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Abstract

Background: Chronic Kidney Disease (CKD) is an irreparable long-term illness. CKD influences circulatory dysfunction, anemia, malnourishment, strength degeneration, muscle integrity, glucose imbalance, and decreased bone thickness. Some parameters are more important to monitor than others during physical activity.

Aims: The aim is to identify what biochemical parameters are affected during physical activity in the CKD. In addition, this work provides baseline data of a collaborative webinar summarizing eating for energy and physical activity.

Literature Review: Physical activity has many benefits; some include increased blood flow to dialysis vascular access, increased heart rate and reduces fluid overload. Physical activity can also decrease urea and prepares the immune system for transplantation.

Methodology: The research team had several Skype communications to highlight what physical activity and nutrition understanding could be provided to patients (HD and post-transplant patients) through an open webinar via the Renal Patient Support Group (RPSG). The team decided to keep the information generic, real-life and to provide best practice so CKD patients and careers would benefit the most. The webinar was planned for 30-min plus 15 min for potential questions and answers, respectively.

Results: In December (2018), the research team formally introduced a Wellness and Nutrition webinar to the RPSG membership via its 'closed' Facebook social media platform. This webinar was well attended and had over 1000 views following initial 'broadcast', and 27 shares. This was also the first webinar of its kind.

Discussion: Future practice should consider providing context relating to laboratory parameters and physical activity following health consultations.

Recommendations: Involving healthcare scientists, to provide patients with an understanding of laboratory parameters in CKD patients would be advantageous.

Conclusion: There should be more collaboration to enhance practice beyond the clinical environment and a call for more multi-disciplinary 'outside the box' working. Live webinars would support part of joined-up healthcare.

Keywords: Nephrology; Chronic kidney disease; Physical activity; Nutrition; Physiology; Biochemistry

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Introduction

Physical activity has been known to produce various benefits physiologically and psychologically. Post-transplant, although there are initial potential phases where physiologically the allograft is adapting to the immune system, overall the benefits of regular physical activity include: 1) Prevents atherosclerosis (especially low density lipoproteins leading to Cardiovascular Disease -CVD), hypertension and diabetes related complications, 2) Increases heart rate; thus ultimately a decrease in Arterial Blood Pressure (ABP) and reducing oedema/pitting in the ankles, 3) Physical activity prompts a more productive transplant organ owing to increased heart rate, 4) Physical activity reduces stress, frustration and depression, 5) Physical activity increases β-endorphin hormone, causing a state of 'feeling good' and 6) Physical activity is a positive coping strategy [1-3]. This now means CKD patients should be encouraged to keep active.

CKD patients must be careful to some extent with physical activity (at least in the early phase post-transplant) because of the potential changes in creatinine and other important laboratory parameters. Because the transplant allograft is 'foreign', it is vulnerable and should not be compromised.

Several investigations have evaluated exercise in the CKD population [1,2] inform physical activity results in improved performance and health in patients with this illness. Several studies suggest that cardiovascular risk factors such as high blood pressure, hypertrophy, and oxidative pressure could improve with physical activity in this population [2]. Intriguingly no study has reported worsening of kidney function a result of exercise. Exercise appears to be safe in this group if begun at moderate intensity and increased gradually. The evidence suggests that the risk of remaining inactive is higher [2]. One review has summarized End-Stage Renal Disease (ESRD), physical activity and elucidation of its effects on biochemical and haematological parameters in Haemodialysis (HD) patients [4]. Table 1 summarizes 5 stages of CKD.

Aim

In addition to providing some basic background of laboratory markers in CKD patients, this work highlights what biochemical parameters are affected throughout exercise in renal patients. This work will also provide baseline data of a collaborative webinar summarizing eating for energy and physical activity.

Clinical Chemistry Parameters

Creatinine

Transplanted patients tend to be anxious about the creatinine parameter, owing to the risk of developing Acute Allograft Rejection (AAR). The psychological implications of this are yet to be to be studied further [4-6]. Creatinine/renal function is significantly different post-transplant when compared to the HD patient, simply because as with normal renal function, a renal allograft can process up to 180 liter of blood daily, whereas a patient on a form of Renal Replacement Therapy (RRT), even at maximum adequacy will only turnover about 100 liter of blood and this is only during times the patient is on treatment; other periods will be considerably reduced [4-6]. For CKD patients who are active and enjoy keeping fit and healthy, the immediate post-transplant phase can be frustrating and challenging because of 'abnormal blips' in creatinine, urea and immunosuppression dosing. Although post-transplant patients can participate in physical activity, in the immediate phase, this activity should be light so that the transplant and cardiovascular system adapt [4-6]. Creatinine is still the best routine blood test for monitoring renal function. It is a byproduct of muscle breakdown and ultimately excreted by the kidneys. It can be higher in muscular people. Creatinine Clearance (CrCl) is a challenging measure for renal function (but it is helpful); it requires a 24 hour urine collection [4-9].

Urea

Urea is a small protein based chemical that is excreted by the kidneys in normal renal function; urea levels increase when renal function declines [6]. It is synthesized by the urea cycle reactions of carbamoyl phosphate and ammonium, which are derived from deamination reactions [6]. It is not such an accurate kidney function test as creatinine but is a useful test when used in conjunction with creatinine because it is affected by muscle breakdown, how much protein consumed, and whether a patient has consumed enough fluid (rises if dehydrated). The normal range =2.5 mmol/l to 7.1 mmol/l (7 mg/dl to 20 mg/dl) [4-6,8,9].

Potassium

Potassium is a mineral important for the fluid balance in the body and for normal functioning of the heart, kidneys and other organs to function normally. Potassium is found in fruits such as bananas and most people get all the potassium they need from a healthy, balanced diet that includes fruits, vegetables, and protein. Too much potassium can be harmful, especially for CKD patients or those taking specific drugs to treat high blood pressure [6]. Potassium in the nervous system is critical to maintaining normal electrical heart rhythm and normal electrical signals. In the UK, the normal potassium level in the blood is 3.5 mEq/L to 5.0 mEq/L. Potassium levels between 5.1 mEq/L to 6.0 mEq/L are mild hyperkalemia [6].

Calcium

Total and free calcium concentration is characterized by a high physiological variation, depending on age, sex, physiological condition (e.g. pregnancy), and even seasonal variation (due to seasonal variation of vitamin D, which is directly involved in calcium concentration regulation) [6]. Calcium is ultimately important for muscle contraction [4-9].

Haematological Parameters

In CKD, serum iron, transferrin, the iron binding volume, saturation and ferritin are normal. The non-haem Iron absorption from the intestine is also normal, as highlighted in iron kinetics studies [4-9]. It was suggested that a decoupling between the endocrine and the excretory function of the kidney is more responsible than its inability to produce erythropoietin, given the increased levels that can occur in CKD patients with acute anaemia or hypoxic hypoxia [10].

The improvement of anaemia after dialysis is first described in 1970, resulting in the presence of uraemic of erythropoiesis inhibitors in the plasma. Polar lipids, arsenic, spermine and spermidine, vitamin A, and the parathyroid hormone are substances suggested as uraemic inhibitors. An overload of aluminium in dialysis patients is also suggested to cause microcytic anaemia, possibly by inhibiting the erythroid marrow as a result of transferrin binding [11,12]. Each dialysis procedure involves a certain amount of blood loss, which amounts to 4 ml to 20 ml, with an additional loss resulting in frequent blood sampling. A patient on dialysis may lose more than 2 mg of iron a day. In addition, chronic infection and inflammation play an important role in anaemia pathogenesis [13].

A study has identified apparent microcytic hypochromic anaemia in HD patients [14] and another study revealed normocytic normochromic anaemia in 81% of HD patients [15]. The uraemic bleeding pathogenesis was not fully understood. There have been no major changes in plasma coagulation factors and the fibrinolytic system does not seem to be impaired. Ecchymosis, purpura, epistaxis, and bleeding from venepuncture sites are common haematological manifestations of uraemia. There may also be cardiac tamponade after pericarditis and pleural effusion. A major complication is spontaneous subcapsular haematoma of the liver, as are subdural haematomas. Uraemic bleeding has also been attributed to a quantitative platelet reduction in 20% to 52% of the cases [16]. The exact mechanism behind the elevated Erythrocyte Sedimentation Rate (ESR) in ESRD is not linear [17,18]. The haematology in ESRD patients has been summarised [3].

Erythropoiesis in CKD

Among patients with CKD, there is a relative deficiency in erythropoietin production, and this is the main reason that anaemia develops. Other factors that may contribute include iron deficiency, blood loss, inflammation, haemolysis, and nutritional deficits [19]. However, the central role of erythropoietin deficiency is well documented and best demonstrated by the consistent and robust improvement in Hb concentrations after treatment with Recombinant Human Erythropoietin (rHuEPO). Surprisingly, serum erythropoietin concentration is often not reduced in CKD [19], except in relation to the degree of anaemia present. However, as CKD progresses, erythropoietin deficiency becomes more pronounced and the decline in serum concentrations parallels kidney excretory functional loss [19].

Nephrotoxicity and Polypharmacy

Immunosuppression

Pathological changes more so than physical in the early phase post-transplant can be determined by a renal biopsy if there is a risk of AAR. The probability of AAR is reduced later post transplant, because the organ will have adapted [7,8]. Post transplantation, particularly the early period, for many patients, it's challenging to change 'habits' after a period of being on a long term dialysis regimen. Post transplant, understandably patients encounter various drug regimens; monitoring of creatinine, urea, and immunosuppression efficacy because in the initial 6 months post-transplant, patients are at risk of acute rejection, (i.e., cellular, humoral or vascular rejection) [7,8,20]. There are some differences between renal practices and centers with parameters and results this can add burden to patient psychology [7,8,20]. It has been highlighted that CKD patients experience disturbing side effects of immunosuppression drugs, some of which may be attenuated or improve physical activity [1]. Data informs that physical activity post transplant increases physical activity capacity and muscle strength; this also contributes to better wellbeing post transplant [20].

Corticosteroids

Post-transplant patients can be on high dose steroids for some time and so it is more important to take note that in the early phase post transplant light physical activity should be encouraged to keep the heart fit as possible. Steroidal treatment will compromise the cardiovascular system. Patients will be on steroid treatment in the long term and become prone to osteoporosis, so physical activity should be encouraged so joints and muscles can stay healthy and strong [7].

Anti-hypertensives

Hypertension is generally defined as blood pressure >140/90 mmHg in transplant recipients or likewise if CKD patient is treated with anti hypertensive medications [21,22]. A cut-off at 150/90 mmHg has been proposed [23]. Some centres use the blood pressure criteria of the World Health Organization/International Society of Hypertension (>130/85 mmHg) [24]. Besides the blood pressure lowering effect of Calcium Channel Antagonists (CCA), these drugs also effectively counteract the vasoconstriction with CsA treatment (and possibly FK506) [25]. The effect on renal haemodynamics may also reduce long term immunosuppressive nephrotoxicity [26]. Clinical studies have suggested that the use of CCAs in renal transplant patients with CsA may be associated with a reduction in both delayed grafting and acute episodes of rejection, (and possibly also prolong graft function). However, a Meta analysis of [21] studies published in 1994 concluded that results were conflicting [27].

CCAs and ACE inhibitors reduce hypertension to a similar extent in CKD patients [28]. In order to evaluate the effect of CCA and ACE inhibitors on renal allograft function one team performed a double-blind randomized study comparing nifedipine with lisinopril. The aim was to examine graft function (GFR - 99 mTc-DTPA) during a 2-year treatment period [28,29]. The results informed that controlled release nifedipine significantly enhanced renal function by ~20% during this period. In this context it was superior to lisinopril in the treatment of hypertension [30]. These findings agree with those of larger randomized studies [31,32].

Why is Physical Activity Important?

Physical activity, psychology, and immunology

One review considers six aspects of patient recovery and rehabilitation: 1) Psychiatric sequelae, 2) Functional recovery, 3) Stress and coping, 4) The psychological impact of failed kidney transplants, 5) Wellbeing, and 6) Adherence with medications [33]. The research concludes that while studies have become more ambitious and rigorous, there is a pressing need to move from descriptive research to carefully designed multidisciplinary intervention studies with patients with kidney transplants [33].

Physical activity increases the number of circulating lymphocytes and lymphocyte subsets (including NK cells), followed by decreases in cell counts during recovery from physical activity; this lymphocytopenia (low lymphocyte count) appears to be owing to a decrease in percentage of type-1 T-cells and NK-cells in circulation at this time. T-cell proliferation and T-cell production of IL-2 and IFN-gamma is immediately reported after acute, intense exercise [33]. After physical activity, it does NK Cell Activity (NKCA) per cell does not appear to alter unless the bout is prolonged and stressful, in which case NKCA can be depressed for several hours [33]. Resting immune function in athletes is not very different from non-athletes. However, intensified training periods in already well-trained athletes can lead to immunity depression in the resting state [33].

The cumulative effects of repeated seizures of intense physical activity result in increased stress hormones, particularly cortisol and anti-inflammatory cytokines (e.g. IL-6, IL-10). This causes temporary blockage of type-1 T-cell cytokine creation with a relative dampening of the type-I (cell-mediated) response [33].

Physical activity and cytokines

One team demonstrated that physical activity leads to a reduction of the percentage of type-1 T-cells [34]. This team investigates the mechanisms underlying the physical activity-induced shift in the balance between type-1 and type-2 cytokine-producing cells [34]. Seven healthy men performed 1.5 h of treadmill running with blood samples drawn before physical activity, at the end of physical activity, and 2-h after physical activity. Intracellular migration of IFN-gamma, IL-2, and IL-4 was detected in CD4(+) and CD8(+) T-cells after stimulation with phorbol 12-myristate 13-acetate and ionomycin [34].

During post-exercise activity period, intracellular expression of IFN-gamma within CD8(+) cells were reduced compared to values obtained immediately after physical activity, whereas the expression of IL-2 and IL-4 did not change within the CD4(+) and CD8(+) cell populations [34]. The decrease in IFN-gamma producing CD8(+) T-cells post physical activity has been negatively correlated with a decrease in memory percentage T-cells within the CD8(+) cells. The study demonstrates that the physical activity induced change in type-1 cytokine producing T-cells is related to a decline in memory cells [34].

In another study, one team examines the effect of physical activity and adrenergic blockade on lymphocyte cytokine production [35]. Six men ingested either a placebo (control) or an alpha- (Prazosin hydrochloride) and beta-adrenoceptor antagonist (Timolol maleate) capsule (blockade, or BLK) 2 h. Before performing 19 min of bicycle physical activity. Blood was collected before and after physical activity, stimulated with phorbol 12-myristate 13-acetate and ionomycin, and surface stained for CD3(+) and NK CD3(-) lymphocyte surface antigens. Cells were permeabilized, stained for the intracellular cytokines' interleukin IL-2 and interferon IFN-gamma, and analyzed using flow cytometry [35]. Results showed BLK had no effect on the resting concentration of stimulated cytokine-positive T and NK lymphocytes or the amount of cytokine they were producing [35]. Physical activity resulted in an increase in the concentration of stimulated T-and NK-lymphocytes producing cytokines in the circulation, but these cells produced less cytokine post compared with pre physical activity. BLK attenuated the elevation in the concentration of lymphocytes producing cytokines during physical activity [35]. These findings suggest that adrenergic stimulation helps the concentration of lymphocytes in circulation; however, it does not appear to be responsible for the physical activity induced suppression in cytokine production [35].

Prolonged temporary functional immune impairment follows severe physical activity. Low numbers of CD4(+) T-Helper (TH) and CD8(+) T-cytotoxic cells are found in the circulation [36]. Based on the cytokine profile, these cells can be divided into type 1 (Th-1 and Tc-1), which produce interferon-gamma and interleukin IL-2, and type-2 (Th-2 and Tc-2) cells, which produce IL-436. In the study, the question was whether physical activity affected balance between cytokine - producing T-cells.

Nine male runners performed a 2.5 h treadmill exercise at 75% of maximum oxygen intake [36]. Cytokine intracellular expression has been detected post-stimulation of ionomycin and phorbol 12-myristate 13-acetate in blood before, during, and after physical activity. The percentage of type-1 T-cells in the circulation was suppressed at the end of physical activity and 2 h post physical activity, whereas no changes were found in the percentage of type-2 T-cells [36]. Plasma epinephrine is negatively correlated with circulating percentage CD8(+) T-cells producing IL-2, whereas peak IL-6 correlated with the percentage of CD8(+) IL-4-producing T-cells in the circulation. Peak plasma IL-6 correlated with plasma cortisol post-running [36].

Post-physical activity decrease in T-lymphocyte number is accompanied by a more pronounced decrease in type-1 T-cells, which may be linked to high plasma epinephrine [36]. Furthermore, IL-6 may stimulate type-2 T-cells, thereby maintaining a relatively unaltered percentage of these cells in the circulation compared with total circulating lymphocyte number [36]. In response to physical activity, both CD4(+) and CD8(+) T-cells are mobilized to the blood, but the levels of these cells decline below pre- physical activity values in the post- physical activity period. T-cells are functionally polarized, depending on the cytokines they produce. Type 1 cells produce, (e.g. interferon INF-gamma), whereas type-2 produce, (e.g. interleukin IL-4) [36].

Intense physical activity on T-lymphocytes

The effects of intensified training period (ITP) were examined on type 1 and type 2 T-lymphocyte distributions and intracellular cytokine production [37]. Acute exhaustive physical activity before and after 2 weeks of ITP recovery, but not immediately after ITP, the circulating percentage and number of l FN-gamma (+) (type 1) T-cells [37]. In addition, the amount of IFN-gamma produced by stimulated T lymphocytes was decreased post- physical activity during each trial [37]. The percentage of IFN-gamma+ T-lymphocytes was decreased at rest immediately after the ITP compared to 2 weeks before and after ITP recovery [37]. Neither acute physical activity nor chronic physical activity training caused an alteration in the circulating percentage or number of IL-4+ (type 2) T-lymphocytes. These findings suggest a possible mechanism for increased incidence of chronic infection during physical activity training *via* inflection of type 1 or type 2 T-lymphocyte distributions [37].

Physical activity and hormones

One team assessed Epinephrine (EPI), Norepinephrine (NE), cortisol, lymphocyte sub-population changes, and percentages of CD11a(+), CD11b(+), and CD62L(+) lymphocytes to a 20 min treadmill physical activity of an intensity equal to 80% of the individual's Vo2 [38]. The physical activity was conducted before and after 6 weeks of endurance training consisting of a 1 h run four times a week after 5 days of rest in 10 healthy males [38]. This team did not identify any significant changes in the basal levels of EPI, NE, and cortisol in the plasma, nor in the immune parameters after duration and bed rest [38]. The physical activity test resulted in a significant increase in the levels of EPI and NE after exercise and bed rest. The team also identified a significant increase in cortisol after bed rest, an increase in absolute numbers of leukocytes, granulocytes, monocyte, CD3(+), CD4(+), CD8(+), CD16(+), CD19(+) lymphocytes, percentage of CD11a(+) and CD11b(+) lymphocytes, and to a decrease of CD62L1 before, after physical activity duration, and after bed rest [38]. The team found comparable changes in all measured immune parameters after physical activity time and bed rest. This team informs that repeated stress-induced elevation of EPI and NE was not associated with impairment in the redistribution of immune cells found in response to a single outbreak of physical activity. Table 2 provides a summary of physical activity and hormones [38,39].

Table 1: Stages of Chronic Kidney Disease (CKD) [49].

CKD Severity	CKD Classification
Stage 1	Kidney damage with normal or raised GFR (greater than 90 ml/min/1.73 m^2)
Stage 2	Kidney damage with normal or raised GFR (60-89 ml/min/1.73 m^2)
Stage 3	Moderately impaired GFR (30-59 ml/min/1.73 m^2)
Stage 4	Severely impaired GFR (15-29 ml/min/1.73 m^2)
Stage 5	End Stage Renal Failure or GFR (less than 15 ml/min/1.73 m^2)

CKD is classified in five stages, according to the level of kidney damage and the ability of the kidneys to filter blood. The glomerular filtration rate (GFR) measures the amount of blood that passes through the tiny filters in the kidneys, called glomeruli, each minute. As the disease progresses the GFR falls. Stage 3 is divided into two parts - stages 3A and 3B (but classification for these two sub-divisions is not outlined here).

Table 2: Summary of Physical Activity and Hormones [20].

Summary of Physical Activity and Hormones
Different emotions such as anger, frustration are classed as acute stress will cause an activated immune response but not the same as positive stress (motivational stress).
Positive stress (motivational stress) causes an increase in β-endorphin as doe's physical activity.
Other neuro endocrines need to be better established with respect to their effects on physical activity.
Chronic stress and depression seem better defined but still not well established with respect to physical activity.

Methodology

Collaborative webinar-eating for energy & physical activity

Having identified where CKD patients would benefit most, the research teams had several Skype communications to highlight what physical activity and nutrition understanding could be provided to patients (HD and post-transplant patients) through an open webinar. It was decided between the team to implement an educational webinar *via* the Renal Patient Support Group (RPSGs) 'closed' Facebook/social media platform. The (RPSG) has over 8000 members internationally. The team decided to keep webinar delivery generic, real-life and to provide best practice so CKD patients and careers would benefit the most. The webinar was planned for 30 min plus 15 min for potential questions and answers, respectively. The team also seeked to obtain an understanding of key questions that may come from the membership surrounding CKD health from a social media group platform.

Ethics approval

Consideration for the need for ethics approval was made and the Department of Health guidance was consulted (Governance arrangements for research ethics committees 2012). Consent for collaborative webinar data was provided by RPSG chief administrators and taking further consideration of General Data Protection Regulation (GDPR). In keeping with this, the research team has not reported any Personal Identifiable Data (PID) (i.e., names, dates of birth, addresses and/or locations) of participants.

RPSG general data protection regulation (2018)

Primarily the RPSG is a closed Facebook support group and this website is an educational/information portal for patients and careers in CKD. The RPSG is covered under Facebook's data privacy and protection policy. The GDPR creates consistent data protection rules across the EU. The GDPR has been in effect as of 25th May (2018) and applies to organizations based in the EU, as well as to companies around the world who provide or offer goods or services, and who process data from or about people in the EU. In keeping with GDPR, the research teams have not reported any Personal Identifiable Data (PID) (i.e., names, dates of birth, addresses and/or locations) of participants. Supplementary 1 summarizes RPSG background.

The time frame for attending online webinar was limited to 30 min only and therefore a sample size calculation was not carried out, instead a target of 1000 responses was set. It was important to get representation from various ethnicities using the RPSG, and the webinar details was 'pinned as an announcement' over the planned duration.

Results

In December (2018), the RPSG and Renal Mate formally introduced a Wellness and Nutrition webinar to the RPSG membership *via* its closed Facebook social media platform. 1000 RPSG members attended the online webinar representing a 14% response rate. Being an international support group, the respondents had demographics with varying ethnicity, age range and gender representation. The research team did not seek to Personal Identifiable Data (PID).

Some key questions from attendees included; 1) What are some good healthy snacks for the HD patient; 2) What are some of the possible physical activities that can help manage back pain; 3) How can patients who have been on dialysis for more than 7 years reassess and do better to keep motivated. The team informed it is important to do utmost keep a healthy lifestyle, eat healthy, keep an eye on posture (good posture will help release and alleviate back pain), and it's important to reset mind, goals and ambitions. In addition, it's important to find inspiration patients should identify what inspires to keep active and healthy.

Whilst there is little evidence that highlights how webinars and online learning supports patients in CKD and information providing, this webinar was well attended and had over 1000 views following initial 'broadcast', and 27 shares. This was also the first webinar of its kind. It is anticipated that subsequent RPSG collaborative webinars will involve more health professionals to support patients in CKD on a range of health focuses.

Implications to Practice and Research

There are several reasons for recommending physical activity to CKD patients, including 1) restoration of physical functioning following de-conditioning past experience(s); 2) Majority CKD patients are inactive, 3) The high prevalence of CVD factors that may be modified by regular physical activity; 4) Physical activity will optimize physical functioning following transplant; and 5)

Table 3: Summary of the Literature.

Reference/ Investigation Type	Method	Sample	Main Findings	Comments	Integrity and Relevance	Themes Derived
Painter P [1]	Review	No Sample Research informs that training after transplantation increases physical activity capacity and muscle strength. This may contribute to better QOL after transplantation.	There is still a need to have more rounded studies that explore creatinine clearance (ClCr) post intense/ exhaustive training in CKD transplanted recipients.	CKD patients experience troublesome side effects of immunosuppression medication, some of which may be attenuated or ameliorated with physical activity. Peer to peer support could be progressive.	Important review. This work highlights the importance of CKD patients keeping active post-transplant, especially regarding keep blood vessels open to and from efferent and afferent arterioles and in keeping blood pressure at adequate level	Physical Activity Polypharmacy
Wainwright SP et al. [33]	Literature Review	Considers review on six aspects of patient recovery and rehabilitation: 1) psychiatric sequelae, 2) functional recovery, 3) stress and coping, 4) the psychological impact of failed kidney transplants, 5) wellbeing, and 6) adherence with medications.	The team concludes that although studies have become both more ambitious and rigorous, there is a pressing need to move away from descriptive research toward carefully designed multidisciplinary intervention studies with kidney transplant patients.	Resting immune function is not very different in athletes compared with non-athletes. However, periods of intensified training in already well-trained athletes can result in a depression of immunity in the resting state.	More education surrounding physical activity and CKD patients needed, especially where scientists could provide understanding of how laboratory parameters could be affected, positively or negatively.	Physical Activity Psychology Immunology
Starkie RL et al. [35]	Laboratory Research To examine the effect of exercise and adrenergic blockade on lymphocyte cytokine production, six men ingested either a placebo (control) or an alpha- (prazosin hydrochloride) and beta-adrenoceptor antagonist (Timolol maleate) capsule (blockade, or BLK) 2 h before performing 19 +/- 1 min of supine bicycle exercise at 78 +/- 3% peak pulmonary uptake.	Blood was collected before and after exercise, stimulated with phorbol 12-myristate 13-acetate and ionomycin, and surface stained for T (CD3 (+)) and natural killer [NK (CD3 (-) CD56 (+))] lymphocyte surface antigens. Cells were permeabilized, stained for the intracellular cytokines interleukin (IL)-2 and interferon (IFN)-gamma, and analyzed using flow cytometry. BLK had no effect on the resting concentration of stimulated cytokine-positive T and NK lymphocytes or the amount of cytokine they were producing	Research examines the effect of physical activity and adrenergic blockade on lymphocyte cytokine production. Results suggest that adrenergic stimulation contributes to the physical activity -induced increase in the concentration of lymphocytes in the circulation; however, it does not appear to be responsible for the physical activity -induced suppression in cytokine production.	The decrease in activated cytokine production by lymphocytes provides a mechanism for the immunosuppressive effect of strenuous exercise, but it is not known what effect and how clinical laboratory parameters would be affected following physical activity in CKD patients.	Cytokine and lymphocyte migration throughout general physiology is important in health. Baseline education from scientists could support patients with understanding of how physical activity could have beneficial effects on these parameters as well as creatinine and urea.	Physical Activity Cytokines
Steensberg A et al. [36]	Laboratory Research The question seeked to address whether exercise affected the relative balance between the circulating levels of these cytokine-producing T-cells.	Nine male runners performed treadmill running for 2.5 h at 75% of maximal oxygen consumption. The intracellular expression of cytokines was detected following stimulation with ionomycin and phorbol 12-myristate 13-acetate in blood obtained before, during, and after exercise.	Investigation informs prolonged strenuous physical activity is followed by a temporary functional immune impairment. Low numbers of CD4 (+) T-helper (TH) and CD8 (+) T-cytotoxic cells are found in the circulation. Post-physical activity decrease in T-lymphocyte number is accompanied by a more pronounced decrease in type-1 T-cells, which may be linked to high plasma epinephrine.	The percentage of type-1 T-cells in the circulation was suppressed at the end of exercise and 2-h after exercise, whereas no changes were found in the percentage of type-2 T-cells.	Physical Activity and Cytokine research is important in all areas of health. Baseline education from healthcare scientists could support patients with understanding of how T-cells have a role in physical activity and potential preparation for a renal transplant. Webinars via social media/ patient support groups could be a progressive way forward.	Physical Activity Cytokines
Ibfelt T et al. [34]	Laboratory Research This team investigates the mechanisms underlying the physical activity-induced shift in the balance between type-1 and type-2 cytokine-producing cells. This team demonstrates that physical activity induces a decrease in the percentage of type-1 T-cells.	Seven healthy men performed 1.5-hrs of treadmill running with blood samples drawn before physical activity, at the end of physical activity, and 2-hrs after physical activity.	Study demonstrates that physical activity induces a decrease in the percentage of type-1 T-cells. The study demonstrates that the physical activity-induced change in type-1 cytokine-producing T-cells is related to a decline in memory cells.	Intracellular migration of IFN-gamma, IL-2, and IL-4 was detected in CD4 (+) and CD8 (+) T-cells after stimulation with phorbol 12-myristate 13-acetate and ionomycin.	Intracellular expression of IFN-gamma within CD8 (+) cells was decreased in the post-physical activity period compared with values obtained immediately after physical activity, whereas the expression of IL-2 and IL-4 did not change within the CD4 (+) and CD8 (+) cell populations. T-cells post-physical activity negatively correlates with a decrease in percentage of memory T-cells within the CD8 (+) cells. Baseline education from scientists could be important, especially surrounding how T-cell distribution pre and post-transplant for CKD patients. Webinars via social media/ patient support groups could be a progressive way forward.	Physical Activity Cytokines

Lancaster GI et al. [37]	Laboratory Research Team examined the effects of acute exhaustive physical activity/intensified training period (ITP) and chronic physical activity training on type 1 and type-2 T-lymphocyte distributions and intracellular cytokine production	Seven endurance-trained male cyclists completed exercise trials to exhaustion before, immediately after, and following 2 weeks of resting recovery from a 6-day intensified training period (ITP). During each trial, resting and post-exercise blood samples were incubated with phorbol 12-myristate 13-acetate (PMA) and ionomycin and stained for T lymphocyte surface antigens (CD3). Cells were then permeabilized, stained for intracellular cytokines and analyzed using flow cytometry.	Research informs study examined the effects of acute exhaustive physical activity/ intensified training period (ITP) and chronic physical activity training on type-1 and type-2 T-lymphocyte distributions and intracellular cytokine production.	These results suggest a possible mechanism for the increased incidence of infection reported during chronic physical activity training via modulation of type-1 or type-2 T-lymphocyte distributions.	Baseline education from scientists could be important, especially surrounding physical activity post-transplant for CKD patients. Webinars via social media/ patient support groups could be a progressive way forward. Understanding of laboratory parameters potentially affected in pre-and-post transplant patients should be provided by healthcare scientists.	Intense Physical Activity T-Lymphocytes
Imrich R et al. [38]	Laboratory Research The team looked to assess the responses of epinephrine (EPI), norepinephrine (NE), cortisol, changes in lymphocytes subpopulations, and percentages of CD11a+, CD11b+, and CD62L+ lymphocytes to a 20-min treadmill exercise of an intensity equal to 80% of the individual's Vo (2) max	The exercise was performed before and after 6-weeks of endurance training consisting of a 1h run 4 times a week (ET) and after 5-days of bed rest (HDBR) in 10 healthy males.	Investigation informs that a significant elevation of cortisol after bed rest, an increase in the absolute numbers of leukocytes, granulocytes, monocytes, CD3 (+), CD4 (+), CD8 (+), CD16 (+), CD19 (+) lymphocytes, percentage of CD11a (+) and CD11b (+) lymphocytes, and to a decrease of CD62L1 before, after physical activity duration, and after bed rest.	The exercise test led to a significant ($P<0.001$) elevation of EPI and NE levels after both ET and HDBR, a significant elevation ($P <0.01$) of cortisol after HDBR, an increase in the absolute numbers of leukocytes, granulocytes, monocytes, CD3+, CD4+, CD8+, CD16+, CD19+ lymphocytes, percentage of CD11a+ and CD11b+ lymphocytes, and to a decrease of CD62L1 before, after ET, and after HDBR.	Baseline education from scientists could be important, especially surrounding physical activity post-transplant for CKD patients. Webinars via social media/ patient support groups could be a progressive way forward. Understanding of laboratory parameters potentially affected in pre-and-post transplant patients should be provided by healthcare scientists.	Physical Activity Hormones
Painter P [40]	Review	No Sample Author explores 1) Restoration of physical functioning following deconditioning experienced prior to transplant; 2) Most patients are physically inactivity, 3) The high prevalence of cardiovascular risk factors that may be modified by regular physical activity; 4) Physical activity will optimize physical functioning following transplant; and 5) physical activity may reduce or attenuate side effects of immunosuppression.	Study informs transplant recipients tolerate progressive physical activity training well and can achieve levels of functioning similar or higher than normal individuals.	In order to optimize functioning and overall health in organ transplant recipients, regular physical activity should be prescribed and encouraged as a part of the routine post-transplant care. Peer to peer support could be progressive.	Webinars via social media/ patient support groups could be a progressive way forward. Understanding of laboratory parameters potentially affected in pre-and-post transplant patients should be provided by healthcare scientists.	Physical Activity
Johansen and KL Painter P [2]	Review	No Sample This review covers the rationale for exercise in patients with CKD not requiring dialysis and the effects of exercise training on physical functioning, progression of kidney disease, and cardiovascular risk factors	Research informs patients should be provided education to increase their physical activity when possible and be referred to physical therapy or cardiac rehabilitation programmes when appropriate.	Intriguingly no study has reported worsening of renal function a result of physical activity. Peer to peer support could be progressive.	Physical activity appears to be safe in CKD patients if begun at moderate intensity and increased gradually. The evidence suggests that the risk of remaining inactive is higher. Webinars via social media/ patient support groups could be a progressive way forward. Understanding of laboratory parameters potentially affected in pre-and-post transplant patients should be provided by healthcare scientists.	Physical Activity
Muhammad S [4]	Review	No Sample Review summarizes background of key parameters in Haemodialysis (HD) patients and to identify literature on biochemical parameters which are affected during physical activity in HD patients.	This review places emphasis that closer attention should be paid to monitoring HD efficacy and Kt/V (a measure of haemodialysis efficacy).	CKD Patients will not know how long they will be on either treatment forms and for this reason they should be encouraged (or prescribed) to get involved in fitness programmes, which has obvious benefits. Most of the literature cited favours exercise for the HD patient because ultimately it can improve outlook. Exhaustive exercise does improve HD efficacy and ultimately it can aid in the run up and preparation for a renal transplant, but not all patients will be able to tolerate such advanced activity owing to longer-term effects of HD.	Detailed review of important laboratory parameters in HD/pre-transplant patients.	Physical Activity, Biochemistry Parameters Haemodialysis Pre-Transplant

Greenwood SA et al. [43]	Exercise Rehabilitation Research	Seven-hundred and fifty-seven patient's Retrospective longitudinal analysis of clinical service outcomes. Programme completion and improvement in exercise capacity, characterized as change in incremental shuttle walk test (ISWT), were analyzed with Kaplan-Meier survival analyses to predict risk of a combined event including death, cerebrovascular accident, myocardial infarction and hospitalisation for heart failure in a cohort of patients with CKD	Adding on from [2], research informs renal rehabilitation interventions to improve exercise capacity in patients with CKD could reduce risk of morbidity and mortality.	Physical activity has a positive impact on CKD patients. Rehabilitation interventions to improve exercise capacity in CKD patients may reduce risk of morbidity.	Webinars via social media/ patient support groups could be a progressive way forward. Understanding of laboratory parameters potentially affected in pre-and-post transplant patients should be provided by healthcare scientists.	Physical Activity

Summary of the Literature relating CKD and Physical Activity. The studies here also inform impact of physical activity on immune and endocrine systems highlighting how different laboratory parameters are affected. Literature identified according to study type, methods used, sample (where applicable), main findings, integrity and relevance. Comments were added accordingly, and further themes derived to identify patterns in the literature

physical activity may reduce or attenuate side-effects of ongoing medication [40]. Other factors to prompt physical activity in CKD patients are perhaps more obvious, including: reducing hypertension management; reducing risk of hyperlipidemia and type II diabetes. CKD patients can tolerate physical activity [40] and can achieve levels of functioning similar or higher than normal individuals [41].

In order to optimize overall health in CKD patients, routine physical activity should be prompted and encouraged as a part of ongoing healthcare. Table 3 provides a summary of the literature. Education that surrounds laboratory parameters in CKD patients and physical activity is still grey. Practice and research also need to consider how such education is delivered. Future research needs to consider information providing surrounding laboratory parameters and physical activity wherein patients want more understanding about what they should/should not do (or feel they can/can't do). Future practice and research also need to identify how such education is delivered. Involving healthcare scientists, to provide patients with understanding of laboratory parameters in CKD patients will be advantageous.

Discussion

Specifically, there is no longer a dietary or fluid restriction once transplanted. However, there is close monitoring, surveillance and potential changes in medication in the early post transplant phase. CKD patients are not automatic in participating in routine physical activity. Diet and nutrition after being on a HD regimen is also a lifestyle change [4]. It can perhaps take up to 6 months for creatinine and other laboratory parameters to reach normal reference ranges [1,3,4]. Muscle mass increases with protein intake and this may/ may not have a bearing on creatinine early post-transplant; studies exploring this association are still required, however a healthy allograft will allow good clearance if looked after.

Aspects that surround laboratory parameters in CKD patient's post transplant and physical activity are still grey. Although the suggestion is to take it easy in the early period, individuals can get easily stressed, frustrated, or even depressed because of 'blips' in creatinine or urea results. Physical activity has many advantages and ultimately allows CKD patients to cope. However, wellbeing in CKD patients can be overestimated; psychology plays an important role in this respect [42,43]. Research informs renal rehabilitation interventions to improve exercise capacity in patients with CKD could reduce risk of morbidity and mortality [43]. There should be no harm in aerobic physical activity in the early post-transplant period. Since retrospectively there has been an effort to understand stress on physiology, immunology and psychology [44-60], more is now needed to understand what laboratory parameters are affected in CKD patients and how best to support education surrounding this.

Conclusion

There is a range of literature that relates the physical activity entity with stress and T-cell 'recruitment'. Although some investigations may not be directly related to renal transplantation, compelling evidence shows that physical activity reduces T-cells (CD8 and CD4) [61-75]. There should be more collaboration amongst disciplines for innovative ways to enhance practice beyond the clinical environment and a call for more multi-disciplinary proposals. Studies are also required on understanding pathophysiology of creatinine, urea and protein early period post-transplant. This could be accompanied by investigating physical activity physiology, particularly elaborating on lymphocyte-leukocyte trafficking and AAR.

It is important to note that educational webinars provided by healthcare scientists *via* social media support groups could provide CKD patients respectable basis of laboratory parameters to be aware of pre-and-post transplant. There is a lot of different terminology surrounding physical activity in CKD patient's 20 healthcare scientists/researchers should be encouraged to relate future efforts on supporting CKD patients with education online that supports wider healthcare, more intricately. 'Online Digital Scientists' or e-clinics with a healthcare scientist could be another progressive proposition, where a healthcare scientist could be involved online with patients providing basic understanding to prompt shared-decision making. Webinars could become more routine as part of joined-up healthcare.

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