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ORIGINAL ARTICLE

Exercise-mediated improvement of depression in patients with gastro-esophageal junction cancer is linked to kynurenine metabolism

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ABSTRACT

Background: Exercise may improve depression in cancer patients, yet the molecular mechanism behind this protection is poorly understood. Here, we aimed to explore the link between exercise and regulation of kynurenine (Kyn) metabolism and inflammation in patients with operable gastro-esophageal junction (GEJ) cancer patients, who improved significantly in depression score with exercise training.

Material and Methods: Fifty GEJ cancer patients were allocated to 12 weeks of supervised training twice weekly including interval-based aerobic exercise and resistance training, or standard care. Depression score was evaluated by HADS, and blood samples and muscle biopsies were collected for determination of Kyn metabolism and inflammation across the intervention.

Results: Depression scores decreased by −1.3 points in the exercise group ($p < 0.01$), whereas no changes were observed in the control group. Plasma 3-hydroxykynurenine (HK), a Kyn metabolite giving rise to other neurotoxic metabolites, increased by 48% ($p < 0.001$) in the control group, while exercise training attenuated this accumulation. The production of HK is induced by inflammation, and while we observed no differences in systemic pro-inflammatory cytokines, exercise training ameliorated the treatment-induced intramuscular inflammation. Moreover, exercise has been suggested to convert Kyn to the neuroprotective metabolite, kynurenic acid (KA), but despite marked functional and muscular exercise-mediated adaptations, we did not observe any enhancement of KA production and related enzyme expression in the muscles of GEJ cancer patients.

Conclusion: Exercise training reduced symptoms of depression in patients with GEJ cancer, and this effect was associated with an exercise-dependent attenuation of the inflammation-induced conversion of Kyn to neurotoxic metabolites.

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Introduction

Symptoms of depression are highly prevalent in patients with cancer [1], and treatment-related systemic changes in inflammation and metabolism may add to the incidence and severity of depression in the oncology setting [2,3]. In recent years, engaging cancer patients in exercise training with the aim of controlling disease and treatment-related side effects has gained momentum, and accumulating evidence demonstrates that exercise training can lower symptoms of depression in cancer patients [4,5]. However, the biological mechanisms behind this beneficial effect remain to be determined.

It is well-established that inflammation plays a pivotal role in the development and progression of depression which has been linked to tryptophan (Trp) metabolism [6,7]. More than 95% of the bioavailable Trp is metabolized to kynurenine (Kyn), which upon accumulation in the central nervous system (CNS) may lead to psychological disorders including depression [8]. Importantly, several Kyn metabolites have been demonstrated to have either neurotoxic or neuroprotective effects, and the imbalance between these metabolites has been proposed to be critical for the development of symptoms of depression. Kyn is typically converted by kynurenine 3-monooxygenase (KMO) to nicotinamide adenine dinucleotide (NAD) or quinolinic acid (QA), a potent N-methyl-D-aspartate (NMDA) receptor agonist leading to excitotoxicity in the CNS [9]. However, during physical exercise, Kyn may be converted in the exercising muscles by kynurenine aminotransferases (KATs) to kynurenic acid (KA) [10], which is considered to be neuroprotective, acting as an antagonist of the NMDA receptor and thereby counteracting the neurotoxic effects of QA [11]. Moreover, KA cannot cross the blood-brain barrier, so the conversion of Kyn to KA in the periphery may reduce accumulation of Kyn in the

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CNS [3] comprising an intriguing mechanism-of-action through which physical exercise may improve depressive symptoms, but this is undescribed in patients with cancer undergoing chemotherapy.

We, therefore, performed to the present explorative study to gain insight into the regulation of systemic and muscular inflammation and Kyn metabolism, which have been linked to exercise-dependent regulation of symptoms of depression in healthy people. We utilized biological samples and HADS questionnaires, which were collected in an exercise intervention study performed in patients with operable gastro-oesophagal junction (GEJ) cancer during neoadjuvant chemotherapy. Thus, the aim of the present study was to investigate if changes in depression score were linked to changes in systemic and muscular inflammation and Kyn metabolism with or without concurrent exercise training.

Material and methods

The present study utilized data including patient information, patient-reported outcomes, blood samples and muscle biopsies retrieved from the PeRi-operativE Study of Exercise Training (PRESET) feasibility study. The PRESET study (www.clinicaltrials.gov identifier NCT02722785) was designed to explore the safety and efficacy of structured exercise training before and after surgery in patients with GEJ cancer. The study was approved by the local ethics committee (H-17003961) and the main results have been previously reported [12].

Participants

Patients with stage I–III GEJ adenocarcinoma, scheduled to initiate standard neoadjuvant treatment, were eligible for inclusion. Major exclusion criteria were age: <18 or >80; deemed inoperable following multidisciplinary medical conference; pregnancy; presence of any other known malignancy requiring active treatment; deemed in-eligible for neoadjuvant treatment; WHO performance status >1; physical or mental disabilities precluding physical testing and/or exercise; and inability to read and understand Danish. Moreover, for the present explorative investigation, we excluded subjects who did not have a pre- and a post-assessment, which included evaluation of depression score and fasting blood samples.

Patients were recruited from the Department of Surgical Gastroenterology, Rigshospitalet, responsible for the treatment of operable GEJ cancer for the entire area of Eastern Denmark. Eligible patients were informed of the study during their first visit to the out-patient clinic and signed an informed consent before any study-related procedures were performed

Neoadjuvant treatment

Patients were administered standard neoadjuvant treatment regimens consisting of three cycles of chemotherapy given with intervals of 3 weeks. One cycle of chemotherapy consisted of Epirubicin 50 mg/m^2 i.v. on day 1, Capecitabin 500 mg/m^2 p.o. twice daily for 21 days and either Cisplatin 60 mg/m^2 i.v. (ECX) or Oxaliplatin 130 mg/m^2 on day 1 (EOX). A small number of patients received treatment according to the CROSS regime, which consists of five series of paclitaxel 50 mg/m^2 and carboplatin i.v. in doses titrated to achieve an area under the curve of 2 mg/ml/min given once a week concurrently with radiotherapy 41.4 Gy in 23 fractions 5 days per week.

Procedures

During neoadjuvant chemotherapy, patients were allocated without randomization to an exercise group or usual care control group based on their geographical residence. Patients living within the greater Copenhagen Hospitals area were allocated to 12 weeks of supervised exercise on Centre for Physical Activity Research (CFAS) at Rigshospitalet, and patients living outside of this area were allocated to usual care control. The exercise program, which has been described in detail [12], was conducted in accordance with the principles of training and consisted on average of 2 weekly sessions of 30–45 min of aerobic interval cycling on a stationary bike, followed by resistance training with 4 exercises for the major muscle groups: chest press, leg press, lateral pull and knee extension. Individualization was ensured by initial $Watt_{max}$ test on a stationary bike and a one-repeated measurement (1RM) max test of the four strength exercises, and progression was ensured by mid-intervention assessments.

The control group followed current usual care guidelines including nurse-led follow-up and information on lifestyle-related factors and were allowed to participate in any standard hospital-based or community-based exercise programs. Data collection was performed at pre-intervention, i.e., before the 12-week intervention period, and again at post-intervention, i.e., before surgical resection of the tumor.

Depression and anxiety

Depression and anxiety scores were obtained using the Hospital Anxiety and Depression Scale (HADS) questionnaire which was administered before and after neo-adjuvant chemotherapy in both the EX-group and the CON-group.

Collection of muscle-and plasma samples

During standard preoperative diagnostic laparoscopy in full anesthesia, we collected muscle biopsies and blood samples as pre-intervention samples, and at tumor resection as post-intervention samples. Muscle biopsies of approximately 200 mg per biopsy were excised from m. vastus lateralis using the Bergstrom-technique [13]. The muscle biopsies were immediately frozen in liquid nitrogen and stored at $-80\,^{\circ}$C. The collection of the muscle biopsies was optional with 36 out of 50 patients giving their consent. Due to logistical reasons, we missed the opportunity to collect biopsies in 9 cases, even though the patients had given consent.

Table 1. Baseline Characteristics of Included Participants.

Characteristics	All, $n = 43$	Exercise-group, $n = 18$	Control-group, $n = 25$	p value
Age, years, mean (SD)	64.9 (7.3)	63.8 (8.0)	65.4 (6.9)	0.42
Male sex, no (%)	38 (88%)	15 (83%)	23 (92%)	0.63
BMI (kg/m^2), mean (SD)	28.4 (5.7)	28.8 (5.8)	28.1 (5.8)	0.67
Sedentary§	32 (74%)	15 (83%)	17 (68%)	0.31
ASA classification, no (%)				
1	10 (23%)	7 (39%)	3 (12%)	0.06
2	22 (51%)	6 (33%)	16 (64%)	–
3	8 (19%)	2 (11%)	5 (20%)	–
Missing data	4 (9%)	3 (17)	1 (4%)	–
Clinical Tumor Stage (cTNM), n (%)				
I	5 (12%)	2 (11%)	3 (12%)	0.98
II	30 (70%)	12 (67%)	16 (64%)	–
III	10 (23%)	4 (22%)	6 (24%)	–
Neo-Adjuvant Treatment				
EOX	18 (42%)	7 (39%)	12 (48%)	0.65
ECX	22 (51%)	9 (50%)	9 (36%)	–
CROSS	6 (14%)	2 (11%)	4 (16%)	–

Data is represented as numbers (%) or mean (Standard Deviation).
§Sedentary is defined as reporting less the 150 min moderate intensity physical activity per week.
Abbreviations: ASA: American Society of Anesthesiologists; cTNM: clinical tumor stage; ECX: Epirubicin + Cisplatin + Capecitabin; EOX: Epirubicin + Oxaliplatin + Capecitabin; CROSS: paclitaxel + carboplatin + radiotherapy.

Blood samples were drawn from all 50 patients at pre-intervention (one sample was lost after collection) and from all 46 patients planned for surgical resection of the tumor 12 weeks later. Four patients in the exercise group gave informed consent for us to draw blood samples during an acute exercise session at one of the planned training sessions. A venous catheter was placed in a cubital vein and blood was collected in ethylene-diamine-tetraacetate (EDTA) containing tubes before and immediately after the training session ended.

Analysis of plasma metabolites and cytokines

Plasma concentrations of tryptophan (Trp), kynurenine (Kyn), anthranilic acid (AA), kynurenic acid (KA), 3-hydroxykynurenine (HK), xanthurenic acid (XA), 3-hydroxyanthranilic acid (HAA), quinolinic acid (QA) and neopterin were analyzed using HPLC-MS/MS (Bevital AS, Norway) [14]. The intra-assay coefficient of variance (CV) was 2.9–9.5% for these biomarkers (all samples were analyzed on the same day). Plasma cytokines were measured by Human Pro-inflammatory 5-plex panel from MSD (Meso Scale Discovery, Maryland, USA) according to manufacturer's protocol. For all 5 analytes, intra- and inter-assay coefficient of variation was lower than 5%.

Analysis of muscle biopsies

RNA was isolated from 10–20 mg of snap frozen muscle tissue after homogenizing in the Qiagen Tissue-lyser Retsch, and RNA extraction was performed according to the Trizol-chloroform protocol. RNA concentrations were determined using the NanoDrop1000 spectrophotometer (Thermo Scientific, Massachusetts, USA), and cDNA was synthesized from 250 ng RNA using the High Capacity cDNA Transcription Kit (Applied Biosystems™, Foster City, USA). Primer sequences were designed using the Primer-BLAST tool from NCBI and purchased from TAG Copenhagen A/S. All samples were run in triplicates using Power Up SYBR® Green PCR Master Mix (Life Technologies, New York, USA), 7.5 ng cDNA, 300 nM forward primer and 300 nM reverse primer in MicroAmp® Optical 384-well reaction plates (Life Technologies, New York, USA). qPCR was performed using the ViiA™7 system (Thermo Scientific, Massachusetts, USA): 50 °C for 2 min, 95 °C for 2 min, and 42 cycles of 95 °C for 15 sec followed by 60 °C for 1 min. Gene expression levels are normalized to GAPDH expression, as this household gene showed no differential expression between the groups.

Statistical analyses

The numerical means (standard derivation, SD) and mean differences [95% confidence interval, CI] based on the Wilcoxon signed-rank test are reported in the result section. Non-parametric paired data were analyzed using the Wilcoxon signed-rank test, while unpaired data were analyzed by Mann-Whitney test. Change in $Watt_{max}$ performance and 1RM strength from pre to post-intervention in the exercise group was analyzed using paired students t-test. All tests were two-tailed and significance level set at 0.05. All statistical analyses were performed in GraphPad.

Results

Study participants

From 1 April 2016 to 1 May 2017, 234 candidates were screened for eligibility. A total of 62 were eligible for inclusion, and 50 participants were enrolled in the main study, comprising a recruitment rate of 81% [12]. Subjects, who had a pre-and a post-assessment including the HADS questionnaire and fasting blood samples (18 patients in the EX-group and 25 in the CON-group), were included in the present study. Baseline characteristics and anti-cancer treatment of the study participants are presented in Table 1.

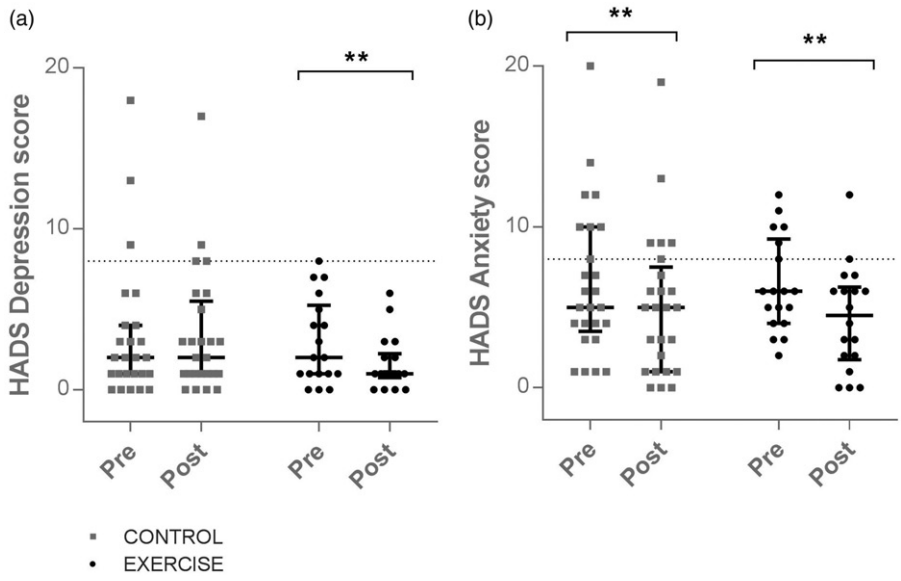

Figure 1. Changes in depression and anxiety scores across 12 weeks of supervised exercise training in patients diagnosed with GEJ cancer. (a) Depression score and (b) Anxiety score according to HADS. The dotted line at score 8 is the cut off for clinical relevant depression or anxiety, respectively. Data are presented as median values and interquartile range, and statistical significance was tested by paired non-parametric Wilcoxon signed-rank test. $^{**}p < 0.01$.

Changes in depression and anxiety scores in GEJ cancer patients

Participation in 12 week of pre-operative exercise training led to a significant decrease in HADS depression score (Mean difference [95%CI]: −1.33 [−2.36; −0.31], $p = 0.01$), although no patients in the exercise-group scored 8 or more at baseline (limit for clinical relevant depression score, Figure 1a). In comparison in the control group, four patients scored 8 or more, and we did not observe difference in pre- and post-depression scores. Across the intervention period, both groups had significant reductions in HADS anxiety scores (EX: −2.06 [−3.51; −0.60], $p = 0.01$; CON: −1.44 [−2.49; −0.39], $p = 0.007$) (Figure 1b).

Trp degradation and conversion of Kyn to KA

The initial step of Kyn metabolism is degradation of Trp to Kyn (Figure 2a). Prior to the intervention, both groups had normal plasma Trp levels, but these dropped below the reference range (43–89 μmol/l) after the intervention in both the exercise group (40.1 ± 10.9 μmol/l) and the control group (37.8 ± 12.1 μmol/l) (Figure 2b). Kyn has been proposed to be metabolized to KA in muscles during exercise. But we did not observe any changes across the intervention period in plasma Kyn or KA levels in either of the groups (Figure 2c and d), even though we found that exercise training led to the expected exercise improvements including 9.5% higher in aerobic fitness ($Watt_{max}$ 12 W [0.07; 23.93], $p = 0.049$) and 22.7% higher muscle strength (1RM leg press 27.0 kg [17.64; 36.25], $p < 0.001$) (Figure 2e and f). In line with the lack of muscular Kyn metabolism, we did not observe any differences in the intramuscular expression of PPAR-α, PPAR-δ, PGC1-α1 or KAT1–3 (Figure 2g).

Conversion of Kyn by KMO to neurotoxic products

As an alternative to the conversion of Kyn to KA, Kyn may be metabolized to 3-hydroxykynurenine (HK) and its downstream products leading to accumulation of neurotoxic metabolites (Figure 3a). We found normal plasma level of HK in both groups at baseline (Figure 3b), but across the intervention period, plasma HK increased significantly in the control group (21.5 μmol/l [5.61; 37.35], $p < 0.001$), while this induction was attenuated in the exercise group across the intervention period (6.42 μmol/l [−0.15; 12.98], $p = 0.07$) (Figure 3b). Accordingly, the ratio of HK/Kyn increased significantly in the control group (8.80 [0.21; 17.39], $p = 0.01$), but not in the exercise group (3.38 [−0.46; 7.21], $p = 0.12$) (Figure 3c). The conversion of Kyn to HK is catalyzed by kynurenine 3-monooxygenase (KMO), an enzyme that is induced by pro-inflammatory cytokines. We, therefore, evaluated the expression level of KMO in muscle biopsies taken post-intervention in both groups and found that KMO expression was higher in the control group compared with the exercise group ($p = 0.05$) (Figure 3d). Across the intervention period, we observed high inter-individual variations in the paired muscle biopsies and thus no significant differences in either group (Figure 3e). HK is either converted to xanthurenic acid (XA) or 3-hydroxyanthranilic acid (HAA), which is formed based on anthranilic acid (AA) (Figure 4a). We did not observe any effects on plasma XA or HAA levels across the intervention period (Figure 3h). In contrast, the HAA intermediate, AA, increased significantly during the intervention period in both the exercise group (3.70 [1.64; 5.77], $p = 0.003$) and the control group (4.21 [1.42; 7.00], $p = 0.002$) (Figure 3g). HAA is further converted to quinolinic acid (QA), and across the intervention period, mean QA levels increased in the control group (60.8 [−35.3; 156.9], $p = 0.045$), while no further increases were observed in the exercise group (Figure 3i).

Systemic inflammation remained unaltered across the intervention period in both groups

Next, we investigated the levels of systemic inflammation in GEJ cancer patients. Neopterin, which is a marker of cellular

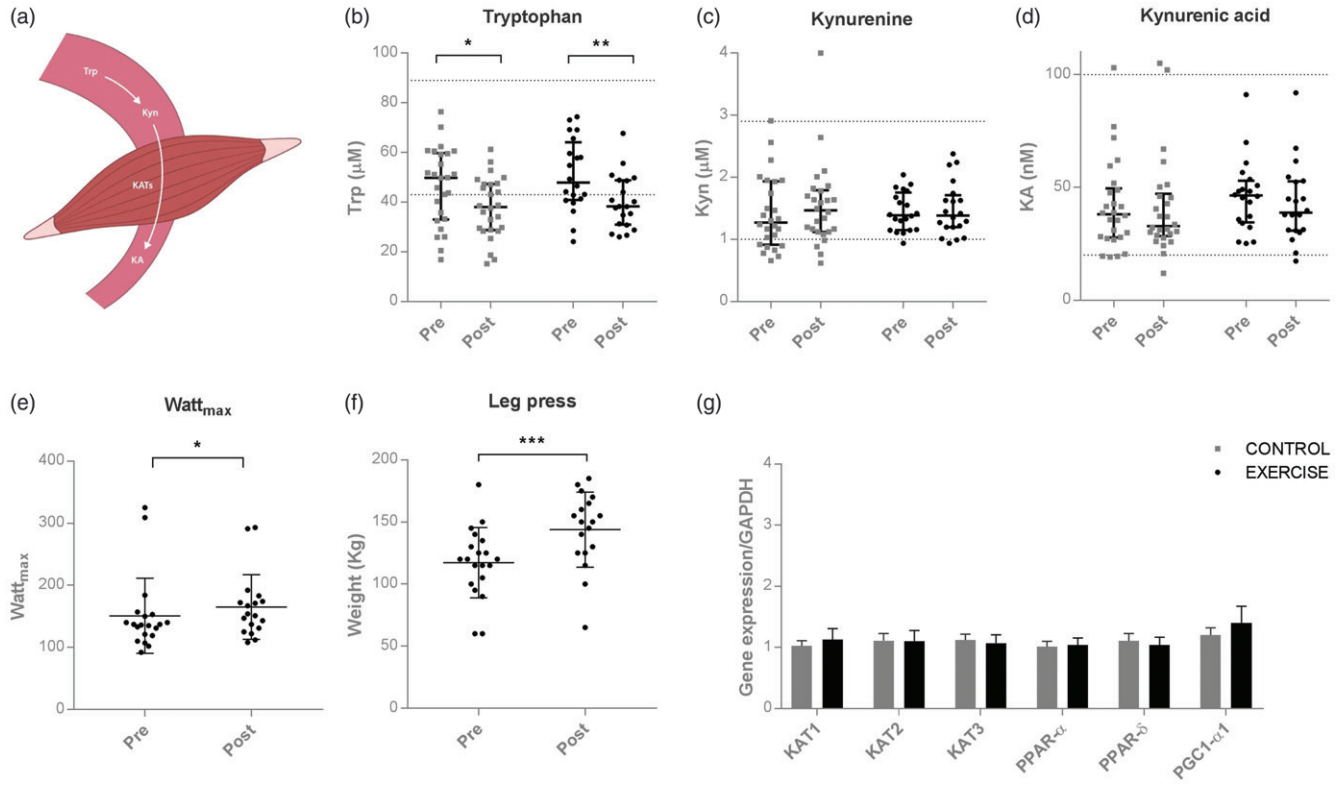

Figure 2. Kynurenine metabolism towards kynurenic acid is not affected by exercise training. (a) Schematic representation of the degradation of tryptophan (Trp) to Kynureninic acid (KA). Plasma levels of (b) Tryptophan (Trp), (c) Kynurenine (Kyn) and (d) Kynurenic acid (KA) before (Pre) and after (Post) 12 weeks of exercise training. The dotted horizontal lines represent the reference plasma levels. Changes in (e) Watt$_{max}$ and (f) 1 repetition maximum (1RM) leg press from pre- to post-intervention in the exercise group (these data were not available in the CON group). Muscular gene expression levels post-intervention of (g) KAT1-3, PPARα, PPARδ and PCG1α1 in the two groups. Data are presented as median values with IQR for b-d, and means ± SD for e.g., Statistical significance was tested by paired non-parametric Wilcoxon signed-rank test. $^{*}p < 0.05$, $^{**}p < 0.01$. KATs = kynurenine-amino-transferases.

immune activation, was not significantly altered across the intervention period in any of the group (Figure 4a). None of the cytokines, TNF-α, IL-6 or IL-10 was induced at the systemic level across the intervention period (Figure 4b–d). In addition, we evaluated the expression of IL-6 in the muscle biopsies and found no difference between the two groups post-intervention ($p = 0.54$, Figure 4e). However, when comparing paired muscle biopsies, we observed a non-significant tendency towards enhanced IL-6 expression in the control group (0.39 [–0.03; 0.79], $p = 0.11$), but not in the exercise group (–0.37 [–1.19; 0.45], $p = 0.23$) (Figure 4f).

Effect of acute exercise on plasma Kyn and KA levels

To explore any acute effects, we evaluated plasma samples from 4 patients taken during an exercise session. We did not observe any effects on plasma Kyn after 60 min of exercise (data not shown). The plasma KA levels tended to increase after 60 min of exercise (13.18 [3.23; 23.12], $p = 0.12$), as did QA levels (111.8 [34.1; 189.4], $p = 0.12$), but no difference in QA/KA ratio was seen (−0.94 [−3.90;2.03], $p = 0.64$).

Discussion

Depression in cancer patients is a multifactorial and potentially debilitation disorder involving psychosocial, biological and even iatrogenic causes, which may be associated with higher mortality risk, impaired quality of life and poor treatment compliance [15–18]. Over the last decade, the role of structured exercise training has gained significant interest as a promising therapeutic countermeasure of depressive symptoms in patients with cancer [19,20], but the underlying mechanisms remain largely unexplored. The principal finding of the present study was that supervised exercise training ameliorated symptoms of depression in GEJ cancer patients and that this at least in part may be explained by a protection against a chemotherapy-induced drive of Trp metabolism towards QA production leading to the accumulation of neuroexcitatory end-products observed in the CON-group. Although this may be just one of several possible psycho-somatic mechanistic exercise-effects, it may have important implications if exercise can be utilized as a targeted countermeasure against inflammation-driven metabolic flux towards QA, occurring secondary to cytotoxic anticancer therapy (Figure 5).

Exercise and symptoms of depression in cancer patients

Here, we found that 12 weeks of exercise training consisting of 30–45 min of aerobic interval training on a stationary bike, followed by resistance training of four major muscle groups could reduce depression scores in GEJ cancer patients. This result is in agreement with previous studies investigating different types of exercise on symptoms of depression in cancer patients [21,22]. Systematic reviews indicate that the beneficial effect of exercise training is mainly restricted to malignancies other than breast cancer [23], while another meta-

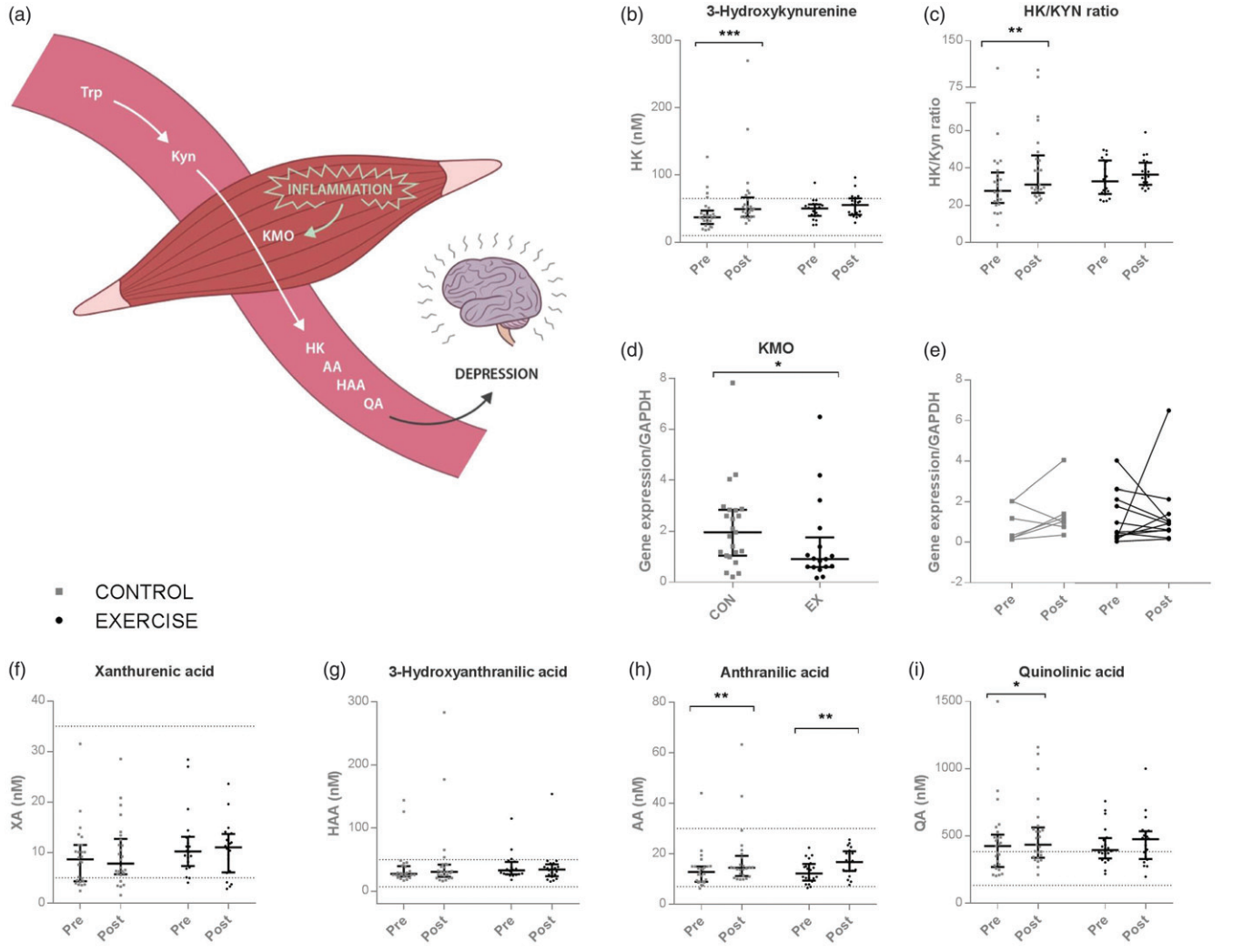

Figure 3. Change in plasma levels of the metabolites in the Kyn-NAD pathway. (a) Schematic representation of tryptophan metabolism through the Kyn-NAD pathway. (b) Plasma level of HK at pre- and post-intervention. (c) The ratio of HK/Kyn in the two groups from pre- to post-intervention. (d) Expression of kynurenine 3-monooxygenase (KMO) in muscle biopsies from the two groups at post-intervention. (e) Expression of KMO in paired muscle biopsies at pre- and post-intervention from the exercise (EX) and the control (CON) group, respectively. (f–i) Plasma levels at pre- and post-intervention of Xanthurenic acid (XA), 3-Hydroxyanthranilic acid (HAA), Anthranilic acid (AA) and Quinolinic acid (QA), respectively. Dotted horizontal lines represent the reference levels. Data are presented as median values ± IQR, and statistical significance was tested by paired non-parametric Wilcoxon signed-rank test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

analysis highlights that this beneficial effect on symptoms of depression was confined to exercise interventions, which were supervised, with session duration longer than 30 min, and not delivered as home-based, all of which were characteristics of the present program, i.e., supervised, hospital-based training with session duration of approximately 60 min. There may be therapeutic elements associated with supervised exercise, including working together with the exercise instructor to acquire new skills, collaboratively setting and achieving exercise goals, and receiving positive feedback and social interaction [24]. In the present study, we cannot separate the impact of supervision from the exercise effects per se, nor determine whether a greater antidepressant effect could have been achieved by optimizing various program components.

Effect of exercise on plasma KA levels

Strong evidence has linked the development of depression to Trp metabolism through conversion of Kyn to neurotoxic end-products [25]. Agudelo and colleagues [10] conducted an elegant study highlighting that exercise-dependent amelioration of depression, resulted from directing the Kyn metabolism towards the formation of KA. To our knowledge, this mechanism has not been investigated in cancer patients. In contrast to the aforementioned study, which included young healthy volunteers, we did not observe any effect of exercise training on plasma Kyn or KA levels. However, our results are consistent with a study in patients with mild-to-moderate depression, where 12 weeks of exercise training were shown to significantly reduce symptoms of depression, but exercise training did not translate into long-lasting changes in plasma levels of Kyn or KA [26].

Effect of exercise and inflammation on the degradation of kyn through the Kyn-NAD pathway

We observed increased levels of the neuroexcitatory metabolites, HK and QA, and the inductions of these metabolites may be attenuated by exercise training. As this pathway is induced by inflammation, the protective effect of exercise might be linked to the anti-inflammatory role of exercise [27]. In particular, the step of Kyn conversion to HK by KMO is induced by pro-

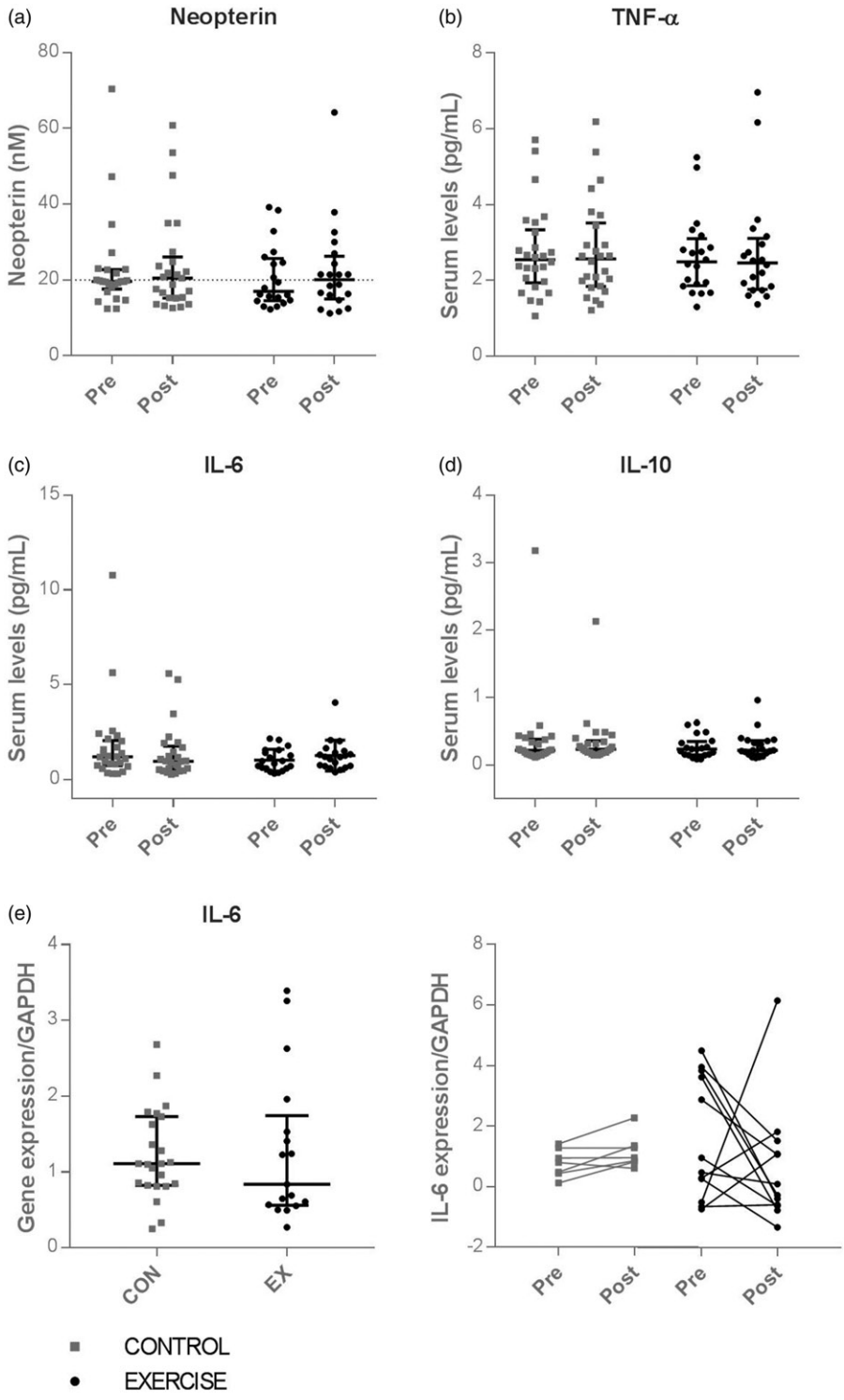

Figure 4. Systemic and muscular inflammatory markers. Plasma levels at pre- and post-intervention of (a) neopterin, (b) TNF-α, (c) IL-6 and (d) IL-10 in GEJ cancer patients. Dotted line in figure (a) represents the reference maximum. (e) Muscle expression level of IL-6 post-intervention in the two groups, and (f) gene expression levels of IL-6 in paired muscle biopsies at pre- and post-intervention in the exercise group (EX) and the control group (CON). Data is presented as median values with IQR, and statistical significance was tested by paired non-parametric Wilcoxon signed-rank test.

inflammatory cytokines. Accordingly, we observed a higher expression of KMO in the control group compared with the exercise group after the intervention. At the systemic level, we did not observe any significant differences in plasma cytokine levels between the two groups, however, in the muscle biopsies, IL-6 expression tended to increase across the intervention period in the CON-group. These findings may suggest that the inflammatory processes occur at the muscular level.

Molecular response in muscle tissue

A notable finding of the present study was that even though our participants showed major functional exercise adaptations with significant improvements in $Watt_{max}$ and muscle strength, we did not observe any molecular adaptations in the expression levels of PGC1-α1, PPAR-α/δ, or KATs in muscle biopsies from the GEJ cancer patients. However, it

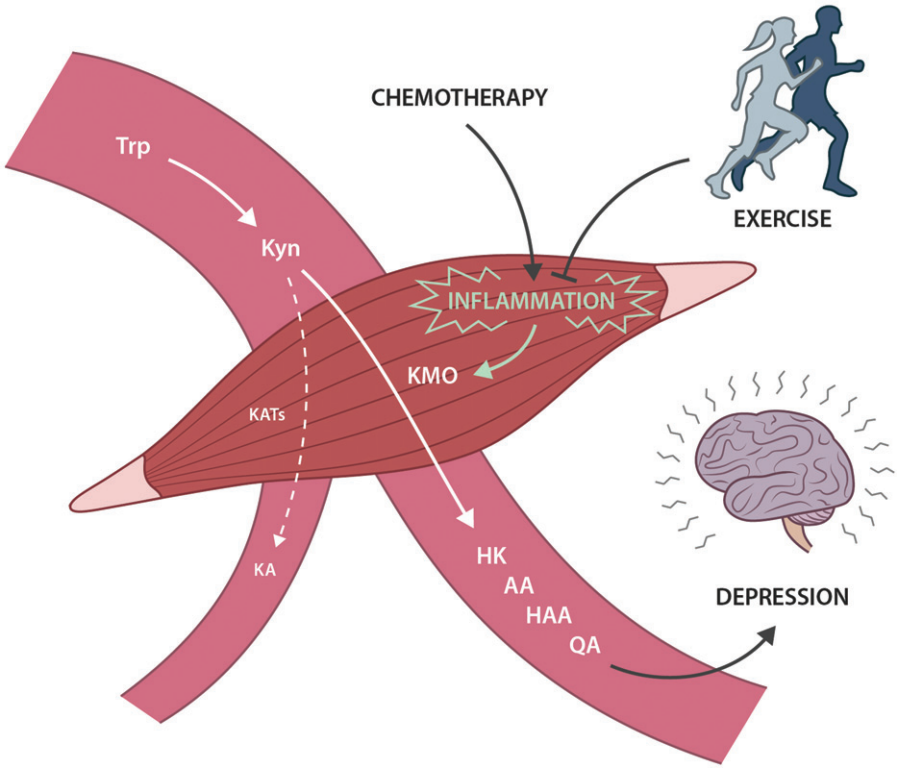

Figure 5. Exercise training during chemotherapy may ameliorate symptoms of depression in GEJ cancer patients. The neoadjuvant chemotherapy can induce intramuscular inflammation, which enhances the drive of Trp metabolism down the Kyn-NAD pathway, leading to accumulation of neuroexcitatory end-products. Our findings suggest that exercise training may attenuate this conversion by possibly regulating, and lowering, intramuscular inflammation.

should be noted that the muscle biopsies were obtained at rest at least 48 h after the last exercise bout, which could explain the lack of changes in PGC1-α1 and PPAR-α/δ. In contrast, up-regulation of the KATs has previously been described in resting muscle biopsies after a training intervention. Few studies have investigated the molecular adaptations in muscle to exercise training in cancer patients, but those who have, show that functional adaptations are poorly reflected by molecular adaptations. For example, patients with germ cell cancer undergoing standard chemotherapy showed physiological adaptations to high-intensity resistance training, but no increase in the number of satellite cells, and no shift in fiber type composition or hypertrophy, which was observed in the healthy age-matched control group [28].

Strengths and limitations

Although the PRESET study was not designed to determine the effect of exercise on depression (nor the mechanistic pathways through which this may be mediated), the study comprised a unique basis to explore these questions. The structured collection of patient-reported outcomes in concert with muscle- and blood samples before and after an exercise period led to the possibility of elucidating if an exercise intervention may lower depressive symptoms through Kyn metabolism by determination of multiple kynurenines, inflammatory factors and expression of relevant enzymes and transcription factors. Important limitations, however, need to be acknowledged, first and foremost the non-randomized trial design, a low number of paired muscle biopsies and acute blood samples. Also, few participants (and none in the exercise group) reported clinical symptoms of depression (HADS-D score >8), and the change in depression score observed in the exercise-group is unlikely to be of clinical relevance. Moreover, the personal contact between the patients and the supervising training instructors should not be underestimated in regard to any effects on depression score.

Conclusion

The present study demonstrates that 12 weeks of supervised exercise before elective surgery may reduce symptoms of depression in patients diagnosed with operable GEJ cancer, and that this effect is associated with an exercise-dependent attenuation of the inflammatory and neuroexcitatory metabolites. These findings underline the beneficial effects of exercise in cancer patients and point to a potential mechanistic explanation for the beneficial effects of exercise on depression, which may guide future anti-depressive interventions for cancer patients in the pursuit of improving the patients' quality of life, compliance to cancer treatment and survival.

Disclosure statement

None of the authors have any conflict-of-interests.

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