Title: Alterations in redox homeostasis during recovery from Unexplained Underperformance Syndrome in an elite international rower

Submission type: Case study

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Abstract

Purpose: This case study of an international rower examines a diagnosis of Unexplained Under Performance Syndrome (UUPS or Overtraining Syndrome) describing a full recovery and return to elite competition the same year. Methods: On diagnosis and 4 and 14 months post-diagnosis, detailed assessments including physiological, nutritional, and biomarkers were made. Results: Clinical examination and laboratory results for haematology, biochemistry, thyroid function, immunology, vitamins and minerals were unremarkable and did not explain the presentation and diagnosis. Redox biomarkers including hydroperoxides, plasma antioxidant capacity, red blood cell glutathione, superoxide dismutase, co-enzyme Q10, vitamin E (α and γ-tocopherol), and carotenoids (lutein, α-carotene, β-carotene) provided evidence of altered redox homeostasis. The recovery strategy began with 12 days of training abstinence and nutritional interventions, followed by 6-weeks of modified training. Four months post-intervention performance had recovered strongly, resulting in the athlete becoming European champion that same year. Further improvements in physiological and performance indices were observed at 14 months post-intervention. Physiologically relevant increases in concentrations of carotenoids were achieved at each post-intervention time point, exceeding the reported critical difference values. Conclusions: We conclude that increasing athlete phytonutrient intake may enhance recovery and tolerance to training and environmental stressors, reducing the risk of unexplained under performance syndrome. Alterations in redox homeostasis should be considered as part of the medical management in unexplained under performance syndrome. This is the first reported case study of an elite athlete with alterations in redox homeostasis in conjunction with a diagnosis of unexplained under performance syndrome.

Introduction

Unexplained Under Performance Syndrome (UUPS) [1] describes an athlete presenting with persistent fatigue in the absence of disease, together with a decline in performance recognised by coach and athlete. This condition is otherwise known as overtraining syndrome. [2] However, UUPS reflects the complexity of the condition, the multi-factorial aetiology, and that imbalances between training load and recovery *may* not be the primary reason for the condition. [1]

Exercise is a source of reactive nitrogen and oxygen species (RNOS), leading to alterations in redox homeostasis (ARH). [3] RNOS are important for adaptation to training, [4] nonetheless, a critical balance (captured in the theory of hormesis) [5] exists between the sufficient or "optimum" dose of RNOS to drive adaptation, and the over-production of RNOS that could lead to apoptosis, immunosuppression, increased fatigue and impaired performance. Oxidative stress (OS) has been observed in athletes diagnosed with OTS [6] and in the context of UUPS and fatigue, it is noteworthy that psychological stress also increases OS. [7]

Olympic class rowing requires large training volumes, involves a long competition season with global travel, and the athlete to make weight; all of which make elite lightweight rowers highly susceptible to UUPS. Some of the largest acute ARH in elite endurance athletes are reported in rowers in the general preparation phase. [3] To date no studies have examined ARH in elite athletes diagnosed with UUPS/OTS.

Case study

The athlete is an experienced international female lightweight rower. She provided written informed consent for the participation in all investigations and the publication of her clinical data.

Medical history, diagnosis, UUPS clinic examination and testing

In the winter general preparation phase, the athlete presented to the Great Britain (GB) Rowing Team Doctor via her coach for suspected UUPS. Heightened fatigue, mood disturbances and a performance decrement that had been evident for several weeks. The athlete reported feeling disengaged with her training and described 'simply going through the motions of training'. In addition, she reported not sleeping well, experiencing disturbing dreams, and becoming emotionally labile. Clinical examination was unremarkable (mental health and/or eating disorders were excluded); carried out by the Chief Medical Officer for GB Rowing (A.R.). No acute infection was reported but the final drop in performance was preceded by a mild viral upper respiratory tract infection. She reported no regular medication. Nutritional supplements were taken as part of the GB Rowing Team nutritional program, consisting of combined carbohydrate and protein, and protein only recovery products, specific micronutrients, and an electrolyte powder. Clinical laboratory results where available (see table 1) were unremarkable apart from serum urea and Epstein-Barr virus (EBV) nuclear antigen, the latter indicative of previous (latent) EBV infection.

Insert table 1 here

Organic disease was excluded and a diagnosis of UUPS was made. A number of investigations were undertaken: Resting venous blood draws for the analysis of hydroperoxides (FORT), plasma antioxidant capacity (FORD), lutein, red blood cell glutathione (RBC GSH), α and γ-tocopherol (see previous methodology [8]): An incremental exercise test on a rowing ergometer. In order to assess the redox response to exercise and provide training intensities for recovery, the rowing ergometer test consisted of two parts: 1) a submaximal discontinuous incremental exercise of 5 x 4 min stages separated by 30s to produce a lactate/heart rate curve. Following a 2.5 min recovery period, a final 4 min maximal stage was completed, whereby the athlete was encouraged to provide a maximal effort, recognising that this may not be possible in the UUPS state. FORD and FORT were assessed following submaximal and maximal exercise and during recovery. Finally, a training history, and nutritional and body composition assessments were undertaken, of which body weight was comparable across all three visits (±1.0 kg), as were skinfolds (± 3.3mm) measured across 8 sites by the same technician; accredited via the International Society for the Advancement of Kinanthropometry. A 5-day written and photographic food diary was analysed using Nutritics© software (Table 2). Three food diaries were collected; the week following her UUPS diagnosis; again at 14 months follow up; and a previous winter training period when healthy via the GB team nutritionist for comparison.

Insert table 2 here

Following completion of her initial physiological and nutritional assessment and biomarker profiling at diagnosis, a number of dietary interventions were

instigated to: 1) facilitate rapid recovery and return to training; 2) prevent relapses; 3) enable improved tolerance of the training load and environmental "stressors". The dietary interventions consisted of dietary protein in the form of un-denatured whey protein (Immunocal™), increased consumption of dietary antioxidants in the form of fruits, vegetables and specific nuts and seeds (recognising the aforementioned foods will also provide proteins, fatty acids, minerals, vitamins and energy), and selective use of an antioxidant supplement as a concentrated source of anthocyanins and melatonin; Cherry Active™.

Physiological testing results

Positive physiological improvements for sub-maximal and maximal exercise were evident at 4 and 14 months post-intervention, indicated by lower blood lactate and heart rate responses for each power output produced (Figure 1).

Insert figure 1 here

Training volume and adherence

Prior to the onset of UUPS, training adherence to winter training comprised 100% of the prescribed training load. On diagnosis, ~12 days of complete rest was advised. Following which, training was resumed at a reduced volume for 6 weeks, with heart rate limits imposed on training sessions to avoid further pro-oxidant stimulus. This was followed by 3.5 weeks of full volume training but utilised alternate modalities at carefully prescribed intensities; normal training resumed at 10 weeks post diagnosis. The period between resuming normal training and winning at the European Rowing Championships, 100% training adherence was achieved.

Case discussion

To our knowledge this is the first documented case of UUPS in an elite endurance athlete, with complete recovery of performance. It is remarkable, that in the same season as being diagnosed with UUPS and failing to complete planned winter training, the athlete became European champion. In addition, we present novel findings of ARH on diagnosis of UUPS and at 4 and 14 months recovery. Moreover, the ARH, most notably the substantial increases in her blood carotenoids at 4 and 14 months post-intervention are of physiological significance based on published critical difference values (CDV), which provide confidence in physiologically relevant biomarker changes. [8]

We believe the athletes' recovery and increased capacity to tolerate OS most notably at 4 months post-intervention (biomarkers of OS remaining high i.e. SOD and FORT) are related to the substantial increases in her serum carotenoid concentrations (>CDV; see table 3). Our assumptions being supported by the following: 1) Blood carotenoid concentrations are valid biomarkers of fruit and vegetable consumption, [9] which were increased via her diet: 2) 2-weeks of reduced fruit and vegetable intake in athletes results in decreases in blood carotenoid concentrations, increases in OS and rate of perceived exertion: [10] 3) The observed changes in blood carotenoids are greater than the reported CDV for the aforementioned biomarkers and therefore of physiological significance:[8] 4) Carotenoids provide a more robust cellular antioxidant defence and response to "stress" through increased scavenging of RNOS and through activation of signalling pathways leading to increased expression of cyto-protective genes. [11] Starting periods of intensified training with higher concentrations

of carotenoids could be advantageous when the physiological and psychological stress is high.

Insert table 3 here

The following factors may have collectively caused overwhelming OS leading to the athlete's diagnosis of UUPS: 1) Pre- and post- world championship psychological stress and associated disturbed sleep; 2) increased winter resistance training load; and 3) upper respiratory tract infection in the week's prior to UUPS. It is well understood, that psychological stress, [7] overload resistance training [12] and infection induce OS. [13] Consequently, chronic OS may have hampered recovery, inducing a state of excessive fatigue. Indeed, FORT concentrations exceeded those reported for elite endurance athletes and well trained athletes in the general preparation phase. [8,14] At 4 months post-diagnosis, FORT concentrations remained elevated, despite recovery of performance, reflecting on going OS. However we submit that a greater capacity to tolerate the OS as a result of substantial increases in the blood carotenoids (and other phytonutrients not otherwise quantified e.g. polyphenols) and dietary advice from the diagnosis of UUPS to recovery, served to protect the athlete through robust cellular defences, enabling her to maintain 100% adherence to the training programme, and restore elite performance.

The strategy of bolstering phytonutrient intake through increasing the dietary supply of fruits, vegetables, nuts and seeds appears to have improved antioxidant defences (nutrients and synthesis of enzymes). We also provided protein in the form of undenatured whey, reported to increase intracellular GSH and influence physical performance. [15] In addition, a concentrated source of anthocyanins in the form of cherries, known to decrease OS. [16] Indeed, the athlete's dietary analysis provides additional evidence for the changes in dietary patterns post-intervention. For example, her dietary intake of vitamin A and vitamin E were 136% and 90% greater at 14 months post intervention than at diagnosis. Of interest, athletes on a 2-week antioxidant restricted diet were reported to consume 976 ± 120 vitamin A ug/d; [10] comparable with her vitamin A intake at diagnosis (table 2). Furthermore, in support of positive behavioural changes in fruit, vegetables, nuts and seeds leading to improved recovery, folic acid (339 mg vs. 277mg), vitamin C (149 mg vs. 65 mg), vitamin E (21 mg vs. 11mg) and fat intakes (121g vs. 72 g) were all greater in recovery, than at diagnosis.

In conclusion, we provide the first evidence of ARH in an elite international rower in association with UUPS. Increasing dietary phytonutrient intake in endurance athletes may enhance recovery from UUPS, and may serve to reduce the future risk of UUPS.

Acknowledgments.

A very special thanks to the athlete included in this case study for supporting the publication of her case study. We continue to wish her success in training, competition and life. Her commitment and dedication to her craft is inspirational. Our thanks also extend to Liz Arnold of GB Rowing for providing information on the athletes training adherence.

Conflict of interest: None

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289 Tables

290 Table 1. Clinical laboratory results and dietary analysis on diagnosis of UUPS and at
291 4 and 14 months post interventions

~~Haematology~~	Units	Range	UUPS	14 months
RBC	10*12/L	3.80 - 5.00	4.49	4.62
Haemoglobin	$g \cdot L^{-1}$	115 – 145	145	145
Haematocrit	$L \cdot L^{-1}$	0.360 - 0.460	0.430	0.436
MCV	$f \cdot L^{-1}$	84 – 98	96	94
MCH	pg^{-1}	27.5 - 32.0	32.3	31.4
MCHC	$g \cdot L^{-1}$	300 - 360	336	333
RDW	%	>14.5	13	13
WBC	$10*9 \cdot L^{-1}$	3.5 - 10.0	5.51	4.70
Neutrophils	$10*9 \cdot L^{-1}$	1.7 - 7.5	3.39	2.20
Lymphocytes	$10*9 \cdot L^{-1}$	1.0 - 3.5	1.61	1.80
Monocytes	$10*9 \cdot L^{-1}$	0.3 - 1.0	0.41	0.60
Eosinophils	$10*9 \cdot L^{-1}$	<0.4	0.07	0.10
Basophils	$10*9 \cdot L^{-1}$	<0.1	0.0	0.0
N/L	$10*9 \cdot L^{-1}$	< 1.0	2.1	1.2
Platelets	$10*9 \cdot L^{-1}$	150 - 400	317	255
Urea	$mmol \cdot L^{-1}$	2.5 - 7.8	8.8	9.2
Creatinine	$umol \cdot L^{-1}$	20 - 107	70	84
Creatine Kinase	$U \cdot L^{-1}$	25 - 320	24	390
Asparate transferase	$U \cdot L^{-1}$	1 - 45	28	53
Alkaline Phosphatase	$U \cdot L^{-1}$	30 - 130	55	54
Alanine transferase	$U \cdot L^{-1}$	1 - 50	28	38
Gamma glutamyl transferase	$U \cdot L^{-1}$	1 - 55	14	10
Total Bilirubin	$umol \cdot L^{-1}$	1 - 25	4	4
Sodium	$mmol \cdot L^{-1}$	133 - 146	142	139
Potassium	$mmol \cdot L^{-1}$	3.5 - 5.3	4.1	5.1
Iron	$umol \cdot L^{-1}$	10.6-28.3	18	
Total iron binding capacity	$umol \cdot L^{-1}$	41-77	71	
Ferritin	$ug \cdot L^{-1}$	25 - 200	36	32
Transferrin saturation	%	20 - 55	26	
Total protein	$g \cdot L^{-1}$	64 - 83	68	
Albumin	$g \cdot L^{-1}$	35 - 50	42	38
C-reactive protein	$mg \cdot L^{-1}$	1 - 10	0.5	0.5
Erythrocyte sedimentation rate	$mm \cdot h^{-1}$	1-10	2.0	
Free T3	$pmol \cdot L^{-1}$	2.6 - 5.7	4.2	4.3
Free T4	$pmol \cdot L^{-1}$	9.0 - 22.0	19.0	12.7
TSH	$mU \cdot L^{-1}$	0.35 - 5.00	2.0	2.3
EBNA IgG antibody	$U \cdot ml^{-1}$	0 - 5	397*	
EBV early Ag Ab (IgG)	$U \cdot ml^{-1}$	0 - 10	<5	
EBV VCA Ab (IgM)	$U \cdot ml^{-1}$	0 -20	<10	
* results suggestive of past (latent) EBV infection				

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294 Table 2. Dietary analysis
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	Pre-UUPS	UUPS#	14 months
Energy (Kcal)	3166	1966	3030
Carbohydrate (g)	432	208	308
Protein (g)	194	134	179
Fat (g)	78	72	121
Vitamin E (mg)	7.2	11.1	21
Vitamin A* (µg)	711	1060	2509
Vitamin C (mg)	171	65	149
Folate (µg)	499	277	339
Vegetable serves per day**	2	2	6
Fruit serves per day **	3	1	3
Nut serves per day**	0	0	1
Seed serves per day**	1	0	2
Protein serves per day	5-6	4-5	6 + 2 serves of un-denatured whey protein

296 *Retinol equivalents; including preformed retinoids from animal foods, and
297 precursor carotenoids from plant foods.
298 ♯ = food diary taken the week following diagnosis, with the athlete undertaking
299 prescribed rest, not training or using any protein & carbohydrate supplements.
300 **median

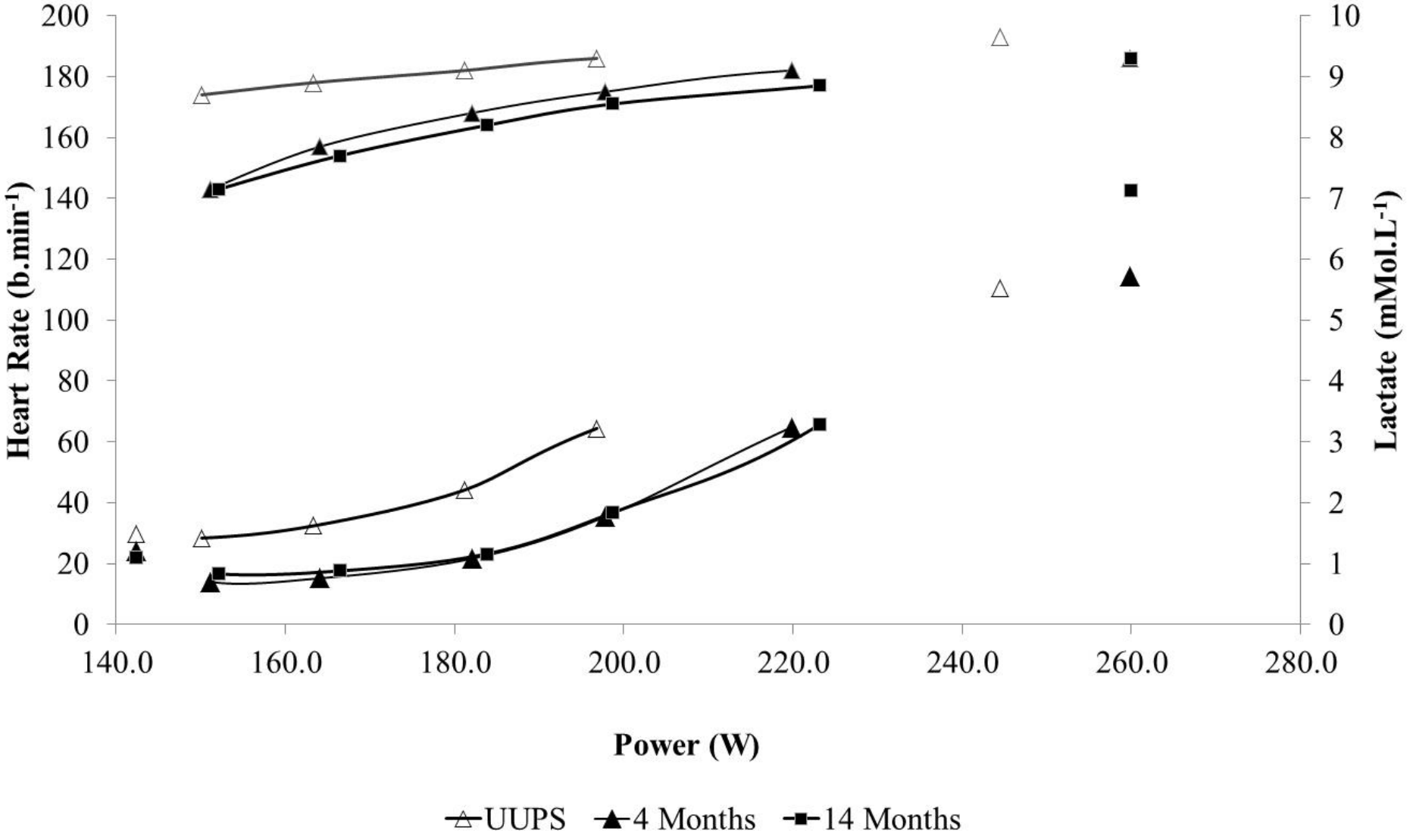
Table 3. Redox measures on diagnosis of UUPS and back in full training (recovered) post intervention

Redox Biomarkers	Laboratory Reference Interval	UUPS	4 months post-intervention	14 months post-intervention	Biomarker change (%) UUPS to 4 months post	Biomarker change (%) UUPS to 14 months post	CDV (%)
FORT	1.22 - 4.56 mmol·L^{-1} H_2O_2	3.01	3.88	1.80	14	-40	17
FORD	0.25 - 3.0 mmol · L^{-1} Trolox	1.69	1.45	1.86	-29	10	24
Co-enzyme Q10	0.55 - 2.0 umol·L^{-1}	0.57	0.51	0.93	-11	63	*
RBC SOD	1102 - 1601 U·gHb^{-1}	1923	1933	1416	<1	-26	*
RBC GSH	1.6 - 2.8 mmol·L^{-1}	2.15	1.89	2.21	-12	3	24
α-tocopherol	25 - 60 mmol·L^{-1}	30.0	24.0	26.0	-20	-13	14
γ-tocopherol	2.0 - 8.5 umol·L^{-1}	1.60	2.08	1.79	30	12	37
α-carotene	0.3 - 1.5 umol·L^{-1}	0.20	1.20	0.46	500	130	107
β-carotene	0.4 - 3.0 umol·L^{-1}	0.52	3.69	1.90	609	265	28
Lutein	0.4 - 1.10 umol·L^{-1}	0.52	1.04	0.94	100	81	13
Total carotenoids	No range umol·L^{-1}	*1.24*	*5.93*	*3.30*	*378*	*166*	*

*CDV = critical difference value; RBC SOD = red blood cell superoxide dismutase; RBC GSH = red blood cell glutathione; FORT = free radical oxygen test; FORD = free radical oxygen defence; * = unknown CDV/not published*

Figure legends

Figure 1. Lactate and heart rate responses to sub-maximal and maximal rowing ergometry when diagnosed with UUPS and repeated at 4 and 14 months post-intervention.


Heart Rate (b.min-1)
Lactate (mMol.L-1)
Power (W)
UUPS
4 Months
14 Months
200
180
160
140
120
100
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