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THE EFFECT OF EXERCISE ON ALCOHOL USE

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ΕΥΧΑΡΙΣΤΙΕΣ

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Αν και η χαμηλή με μέτρια κατανάλωση αλκοόλ θεωρείται ευεργετική για την υγεία, η κατάχρηση αλκοόλ μπορεί να οδηγήσει σε διαταραχές της χρήσης αλκοόλ (ΔΧΑ), να προκαλέσει πολλές ασθένειες και να αποτελέσει προάγγελο τραυματισμών και βίας, με αποτέλεσμα εκατοντάδες χιλιάδες θανάτους κάθε χρόνο παγκοσμίως. Υπάρχουν κάποιες αναφορές ότι η σωματική άσκηση θα μπορούσε να χρησιμοποιηθεί ως εργαλείο στη θεραπεία των ΔΧΑ. Φυσιολογικές και ψυχολογικές θεωρίες έχουν προταθεί για τη δυνητική ευεργετική επίδραση της σωματικής άσκησης σε άτομα που κάνουν κατάχρηση ουσιών. Ένας πιθανός φυσιολογικός μηχανισμός βασίζεται στην απελευθέρωση β-ενδορφίνης (β-Ε) κατά την άσκηση, η οποία μπορεί να προκαλέσει αισθήματα ευφορίας, να βελτιώσει τη διάθεση, να ελέγξει το στρες κ.ά. Ωστόσο, μόνο λίγες μελέτες έχουν εξετάσει την επίδραση της σωματικής άσκησης στη λήψη αλκοόλ σε άτομα με ΔΧΑ, ενώ υπάρχει βιβλιογραφικό κενό όσον αφορά τους φυσιολογικούς και βιοχημικούς μηχανισμούς που εμπλέκονται στη βαριά κατανάλωση αλκοόλ και πως αυτοί οι μηχανισμοί μπορεί να επηρεάζονται από τη σωματική άσκηση. ***Σκοπός:*** Σκοπός της παρούσας μελέτης ήταν: (1) να εξετασθούν οι αποκρίσεις σε οξεία άσκηση σε αλκοολικούς ασθενείς, (2) να εφαρμοστεί και να αξιολογηθεί μια μακροχρόνια επιβλεπόμενη παρέμβαση προπόνησης, με στόχο τη διακοπή της κατάχρησης αλκοόλ από άτομα που κάνουν βαριά κατανάλωση αλκοόλ, (3) να εξετασθεί εάν μια μακροχρόνια επιβλεπόμενη παρέμβαση προπόνησης μπορεί να μεταβάλλει αποκρίσεις σε οξεία και χρόνια άσκηση σε άτομα που κάνουν βαριά κατανάλωση αλκοόλ, (4) να εξετασθούν οι αποκρίσεις σε οξεία άσκηση σε άτομα που κάνουν και σε άτομα που δεν κάνουν βαριά κατανάλωση αλκοόλ. Η έρευνα εστιάστηκε κυρίως στη διερεύνηση της σχέσης μεταξύ άσκησης (οξείας και χρόνιας), υποθαλαμο-υποφυσιακού-επινεφριδικού άξονα και

κατάχρησης αλκοόλ. Επιπλέον, μελετήθηκε και η επίδραση της οξείας και χρόνιας άσκησης σε διάφορους άλλους φυσιολογικούς και βιοχημικούς δείκτες, καθώς και σε δείκτες της αντιοξειδωτικής κατάστασης. ***Μέθοδος:*** (1) Εννέα αλκοολικοί ασθενείς (ηλικία = 41.2 ± 6.7 έτη) και 9 υγιή άτομα ως ομάδα ελέγχου (ηλικία = 38.2 ± 10.7 έτη) έκαναν άσκηση 30 λεπτών, χαμηλής έντασης (55-60% της Μέγιστης Καρδιακής Συχνότητας), σε κυκλοεργόμετρο. Οι ασθενείς είχαν υποβληθεί σε αποτοξίνωση και είχαν διαγνωσθεί ως εξαρτημένοι από το αλκοόλ σύμφωνα με το DSM-IV και τη Δοκιμασία για την Ανίχνευση των Διαταραχών Χρήσης Αλκοόλ (Alcohol Use Disorders Identification Test - AUDIT; AUDIT score > 20). Η καρδιακή συχνότητα καταγραφόταν κατά τη διάρκεια των συνεδριών άσκησης μέσω τηλεμετρίας μικρής εμβέλειας. Συμπληρώθηκε το ερωτηματολόγιο επιθυμίας για αλκοόλ και συλλέχθηκαν δείγματα αίματος πριν και αμέσως μετά την άσκηση. Τα δείγματα αίματος αναλύθηκαν για γενικής αίματος (complete blood count - CBC), γαλακτικό οξύ και (β-Ε). (2) Έντεκα άνδρες (ηλικία: 30.3 ± 3.5 έτη; BMI: 28.4 ± 0.86 kg/m^2) βαρυπότες προσφέρθηκαν εθελοντικά να συμμετάσχουν σε μια επιβλεπόμενη παρέμβαση προπόνησης μέτριας έντασης 8 εβδομάδων (50-60% της Καρδιακής Συχνότητας Εφεδρείας). Όλοι οι συμμετέχοντες έκαναν καθιστική ζωή και συνήθιζαν να κάνουν βαριά κατανάλωση αλκοόλ (πάνω από 14 ποτά ανά εβδομάδα ή 4 ποτά ανά περίσταση, AUDIT score > 8). Κατά τη διάρκεια της παρέμβασης προπόνησης 8 εβδομάδων, οι συμμετέχοντες κατέγραφαν την ημερήσιά τους κατανάλωση αλκοόλ και παρακινιόντουσαν να αυξήσουν σταδιακά τη διάρκεια και τη συχνότητα της εκγύμνασης. Η καρδιακή συχνότητα καταγραφόταν κατά τη διάρκεια των συνεδριών άσκησης μέσω τηλεμετρίας μικρής εμβέλειας. Τα δείγματα αίματος συλλέχθηκαν πριν και μετά από 4 εβδομάδες καθιστικού τρόπου ζωής πριν την παρέμβαση (κατάσταση ελέγχου), την ημέρα πριν την έναρξη της παρέμβασης, στο τέλος της $4^{ης}$ και της $8^{ης}$ εβδομάδας της παρέμβασης, καθώς και 4 εβδομάδες μετά την

παρέμβαση (περίοδος follow up). Τα δείγματα αίματος αναλύθηκαν για γενική εξέταση αίματος, ταχύτητα καθίζησης ερυθρών αιμοσφαιρίων, γαλακτικό οξύ, ασπαρτική τρανσαμινάση, τρανσαμινάση της αλανίνης, γ-γλουταμυλ τρανσφεράση (γ-GT), β-Ε, επινεφρίνη, νορεπινεφρίνη, αδρενοκορτικοτροπίνη, κορτιζόλη, C-αντιδρώσα πρωτεΐνη, ουρικό οξύ, χολερυθρίνη, ολική αντιοξειδωτική ικανότητα και καταλάση. Φυσιολογικοί και άλλοι σχετιζόμενοι με το αλκοόλ δείκτες επίσης εξετάσθηκαν. (3) Οι βαρυπότες, οι οποίοι συμμετείχαν στην παρέμβαση προπόνησης, εκτέλεσαν επίσης 3 δοκιμασίες οξείας άσκησης μέτριας έντασης (50-60% της Μέγιστης Καρδιακής Εφεδρείας): μια δοκιμασία πριν την παρέμβαση προπόνησης, μια δοκιμασία την $4^{η}$ εβδομάδα παρέμβαση προπόνησης και μια δοκιμασία την $8^{η}$ εβδομάδα παρέμβαση προπόνησης. Η καρδιακή συχνότητα καταγραφόταν κατά τη διάρκεια των δοκιμασιών μέσω τηλεμετρίας μικρής εμβέλειας. Δείγματα αίματος συλλέχθηκαν πριν και αμέσως μετά την άσκηση, και αναλύθηκαν για τους ίδιους δείκτες που μετρήθηκαν στην παρέμβαση προπόνησης. (4) Μελετήθηκε επίσης η επίδραση μιας συνεδρίας οξείας άσκησης μέτριας έντασης (50-60% της Μέγιστης Καρδιακής Εφεδρείας) σε βαρυπότες και σε άτομα που δεν ξεπερνούν τα όρια της μέτρια κατανάλωση αλκοόλ. Η καρδιακή συχνότητα καταγραφόταν κατά τη διάρκεια της δοκιμασίας μέσω τηλεμετρίας μικρής εμβέλειας. Δείγματα αίματος συλλέχθηκαν πριν και αμέσως μετά την άσκηση, και αναλύθηκαν για τους ίδιους δείκτες που μετρήθηκαν στην παρέμβαση προπόνησης. ***Αποτελέσματα:*** (1) Τα επίπεδα της β-Ε ήταν σημαντικά χαμηλότερα στους αλκοολικούς ασθενείς από την ομάδα ελέγχου, και σημαντικά αυξημένα ($p<.001$) μετά την άσκηση (πριν: 1.57 ± 0.39 pmol/L, μετά: 4.8 ± 1.6 pmol/L) μόνο στους αλκοολικούς ασθενείς. Τα επίπεδα γαλακτικού αυξήθηκαν σημαντικά και στις δυο ομάδες. Καμία διαφορά στις παραμέτρους της CBC δεν παρατηρήθηκαν μεταξύ των δυο ομάδων, ενώ η άσκηση οδήγησε σε παρόμοιες αυξήσεις στα ερυθρά αιμοσφαίρια, την αιμοσφαιρίνη και τον αιματοκρίτη στις δυο ομάδες. Τέλος,

βρέθηκε μια μη-στατιστικά σημαντική μείωση (περίπου 17%) στην επιθυμία για αλκοόλ στους αλκοολικούς ασθενείς. (2) Η παρέμβαση επιβλεπόμενης προπόνησης 8 εβδομάδων οδήγησε σε μειωμένη κατανάλωση αλκοόλ και επίπεδα γ-GT, καθώς και βελτιωμένη φυσική κατάσταση σε βαρυπότες. Αυτές οι θετικές επιδράσεις διατηρήθηκαν για τουλάχιστον 4 εβδομάδες μετά το τέλος της παρέμβασης προπόνησης. Ωστόσο, δεν παρατηρήθηκε καμία αλλαγή στη β-Ε ή σε άλλες ορμόνες του υποθαλαμο-υποφυσιακού-επινεφριδικού άξονα μετά την παρέμβαση προπόνησης. (3) Η παρέμβασης προπόνησης δεν μετέβαλλε σημαντικά τις αποκρίσεις των ορμονών του υποθαλαμο-υποφυσιακού-επινεφριδικού άξονα των βαρυποτών στην οξεία άσκηση (4) Οι βαρυπότες παρουσίασαν αυξημένα επίπεδα ηπατικών ενζύμων σε σχέση με την ομάδα ελέγχου πριν και μετά την άσκηση, γεγονός που μπορεί να είναι το αποτέλεσμα της βαριάς κατανάλωσης αλκοόλ. Τα επίπεδα β-Ε σε ηρεμία δεν ήταν μειωμένα στους βαρυπότες σε σχέση με την ομάδα ελέγχου. Μετά την οξεία άσκηση, αυξήθηκαν μόνο τα επίπεδα της β-Ε των βαρυποτών και ήταν διπλάσια από αυτά της ομάδας ελέγχου. ***Συμπεράσματα:*** Οι αλκοολικοί έχουν κεντρική έλλειψη οπιοειδών, όπως υποδηλώνεται από τα χαμηλά επίπεδα β-Ε, που δεν είναι εμφανής στους βαρυπότες ίσως λόγω του χαμηλότερου επιπέδου έκθεσης στο αλκοόλ. Προτείνεται ότι η οξεία άσκηση ενεργοποιεί τον υποθαλαμο-υποφυσιακό-επινεφριδικό άξονα και σε βαρυπότες και σε αλκοολικούς ασθενείς. Τα αποτελέσματα υποδεικνύουν ότι η συστηματική άσκηση θα μπορούσε να δράσει ως μια υγιεινή συνήθεια που μπορεί να βοηθήσει άτομα με ΔΧΑ να μειώσουν τη λήψη αλκοόλ και να βελτιώσουν την κατάσταση της υγείας τους.

Λέξεις - κλειδιά: *Β-ενδορφίνη, οποιοειδές σύστημα, διακοπή αλκοόλ, επιθυμία για αλκοόλ, πρόγραμμα άσκησης, βαρυπότες, διαταραχές χρήσης αλκοόλ*

ABSTRACT

Although light to moderate consumption of alcohol is thought to be beneficial for health, heavy drinking can lead to alcohol use disorders (AUDs), cause many diseases and be a precursor to injury and violence, resulting in hundreds of thousands deaths per year worldwide. There are some reports that physical exercise could be used as a tool for the treatment of AUDs. Both physiological and psychological theories have been proposed for the potential beneficial effects of physical exercise in substance abusers. One possible physiological mechanism is based on the release of β-endorphin (β-E) and other endogenous opioids during physical exercise, which can cause feelings of euphoria, improve mood, control stress etc. However, only a few studies have examined the effect of physical exercise on alcohol intake in individuals with AUDs. There is a gap in the literature concerning the physiological and biochemical mechanisms involved in AUDs, and how these mechanisms could be affected by physical exercise. ***Purpose:*** The purpose of the present study was: (1) to examine the responses to acute exercise in alcoholic patients; (2) to implement and evaluate a long-term supervised ET intervention aimed at alcohol abuse cessation in heavy drinkers; (3) to examine whether a long-term supervised ET intervention can change responses to acute and chronic exercise in heavy drinkers. The investigation was mainly focused on the investigation of the relationship among exercise (acute and chronic), the hypothalamic-pituitary-adrenal axis (HPA) and alcohol abuse. Furthermore, the effect of acute and chronic exercise on other physiological and biochemical indices, and markers of antioxidant status was also investigated; (4) to examine the responses to acute exercise in individuals who drink and in those who do not drink heavily. ***Methods:*** (1) Nine alcoholic patients (age = 41.2 ± 6.7 yrs) and 9 healthy controls (age = 38.2 ± 10.7 yrs) exercised for 30 minutes at a low intensity (55-60% of

Maximum Heart Rate) on a cycle ergometer. Patients were undergoing alcohol detoxification, were recruited from a psychiatric hospital, and were diagnosed as being alcohol dependent according to the DSM-IV and the Alcohol Use Disorders Identification Test (AUDIT; AUDIT score > 20). Heart rate was monitored during exercise sessions by short-range telemetry. Alcohol urge questionnaire was filled and blood samples were collected prior to and immediately after exercise. Blood samples were analyzed for complete blood count (CBC), lactic acid and β-E. (2) Eleven (age: 30.3 ± 3.5 yrs; BMI: 28.4 ± 0.86 kg/m^2) male heavy drinkers volunteered to participated in an 8-week supervised intervention of moderate intensity exercise (50-60% of Heart Rate Reserve). All participants were sedentary and used to drink heavily (more than 14 drinks per week or 4 drinks per occasion; AUDIT score > 8). During the 8-week supervised exercise training (ET) intervention, participants were recording their daily alcohol intake and were motivated to increase gradually the duration and frequency of ET. Heart rate was monitored during exercise sessions by short-range telemetry. Blood samples were collected prior to and after 4 weeks of sedentariness before ET intervention (control condition), the day before the beginning of the ET intervention, at the end of the 4^{th} and 8^{th} week of ET intervention, as well as 4 weeks after ET intervention (follow up period). Blood samples were analyzed for CBC, erythrocyte sedimentation rate, lactic acid, aspartate transaminase, alanine transaminase, γ-glutamyl transferase (γ-GT), β-E, epinephrine, norepinephrine, adrenocorticotropin, cortisol, C-reactive protein, uric acid, bilirubin, total antioxidant capacity and catalase. Physiological and other alcohol-related indices were also examined. (3) Heavy drinkers, which participated in the ET intervention, also performed three trials of acute moderate intensity exercise (50-60% of Heart Rate Reserve); one trial before ET intervention, one trial at the 4^{th} week of ET intervention and one trial at the 8^{th} week of ET intervention. Heart rate was monitored during trials by

short-range telemetry. Blood samples were collected prior to and immediately after exercise and were analyzed for the same indices measured in the ET intervention. (4) The effect of a bout of acute exercise of moderate intensity (50-60% of Heart Rate Reserve) in heavy drinkers and individuals that do not exceed the limits of moderate alcohol use was also investigated. Η καρδιακή συχνότητα καταγραφόταν κατά τη διάρκεια της δοκιμασίας μέσω τηλεμετρίας μικρής εμβέλειας. Δείγματα αίματος συλλέχθηκαν πριν και αμέσως μετά την άσκηση, και αναλύθηκαν για τους ίδιους δείκτες που μετρήθηκαν στην παρέμβαση προπόνησης. Results: (1) β-E levels were significantly lower in alcoholic patients that controls, and significantly ($p < .001$) increased after exercise (pre: 1.57 + 0.39 pmol/L, post: 4.8 + 1.6 pmol/L) only in alcoholic patients. Lactic acid levels increased significantly in both groups. No differences in CBC parameters were observed between the two groups, while exercise led to similar significant increases in red blood cells, hemoglobin and hematocrit in the two groups. Finally, a non-significant decrease (about 17%) in alcohol urge in alcoholic patients was found. (2) Heavy drinkers exhibited decreased levels of β-E. The 8-week supervised ET intervention resulted in reduced alcohol consumption and γ-GT levels, and fitness improvement in heavy drinker. These positive effects were maintained for at least 4 weeks after the end of the ET intervention. However, no change in β-E or other peptides of the HPA after the ET intervention was observed. (3) ET intervention did not significantly change the responses of HPA axis hormones to exercise in heavy drinkers. (4) Heavy drinkers showed increased levels of liver enzymes compared to control group before and after exercise, which may have been the result of heavy alcohol drinking. Resting β-E levels were not reduced in heavy drinkers compared to control group. After acute exercise, β-E levels increased significantly only in heavy drinkers and were twice as high in heavy drinkers as in control group. ***Conclusion:*** Alcoholics have a central opioid deficiency as indicated by low plasma b-E levels, which

is not evident in heavy drinkers maybe due to lower level of exposure to alcohol. It is suggested that acute exercise activates the HPA axis both in heavy drinkers and alcohol patients. The results indicate that systematic exercise could act as a healthy habit that can help individuals with AUDs reduce alcohol intake and improve health status.

Key Words: *B-endorphin, opioid system, alcohol cessation, alcohol urge, exercise training intervention, heavy drinkers, alcohol use disorders*

CONTENT

LIST OF TABLES

LIST OF GRAPHICS

LIST OF IMAGES

ABBREVIATION LIST

ACTH: AdrenoCorticoTropin Hormone

ALT: Alanine Transaminase

APA: American Psychiatric Association

AST: ASpartate Transaminase

AUDs: Alcohol Use Disorders

AUDIT: Alcohol Use Disorders Identification Test

BAC: Blood Alcohol Concentration

BMI: Body Mass Index

BP: Blood Pressure

CBC: Complete Blood Count

CNS: Central Nervous System

CRP: C-Reactive Protein

DBP: Diastolic Blood Pressure

E: Epinephrine

ESR: Erythrocyte Sedimentation Rate

GRA: Granulocytes

Hct: Hematocrit

HGB: Hemoglobin

HR: Heart Rate

HRR: Heart Rate Reserved

IPAQ: International Physical Activity Questionnaire

LAC: Lactic ACid

LYM: Lymphocytes

MCV: Mean Corpuscular Volume

MCH: Mean Corpuscular Hemoglobin

MCHC: Mean Corpuscular Hemoglobin Concentration

MHR: Maximal Heart Rate

MON: Monocytes

MPV: Mean Platelet Volume

NE: Norepinephrine

PCT: Plateletcrit

PDW: Platelet Distribution Width

PLT: Platelets

RBC: Reb Blood Cell

RDW: Red blood cell Distribution Width

RPE: Rating of Perceived Exertion

RPM: Revolutions Per Minute

SBP: Systolic Blood Pressure

TAC: Total Antioxidant Capacity

VO_2max: Maximal Oxygen Consumption

UA: Uric Acid

WBC: White Blood Cell

WHO: World Health Organization

WHR: Waist Hip Ratio

γ-GT: γ-Glutamyl Transferase

1. INTRODUCTION

Light to moderate alcohol consumption is considered to be beneficial for health (e.g., Brien et al., 2011; Huang et al., 2010). However, uncontrolled and excessive alcohol consumption can cause negative effects in mental and physical health, and social aspects of humans (Caan & Belleroche, 2002). Alcoholism and other alcohol related disorders are a major health concern. Alcohol abuse is a significant cause of death accounting for about 4.5% of all diseases and injuries worldwide (World Health Organization [WHO], 2011a).

1.1. ALCOHOL USE DISORDERS AND OPIOID SYSTEM

Reports indicate that alcohol consumption influences the activity of the endogenous opioid system (Gianoulakis, 2004). Acute exposure to alcohol has been demonstrated to lead to a fast and transient increase in β-endorphin (β-E) release by the pituitary and hypothalamus (Keith et al., 1986; Thiagarajan et al., 1989) in a dose dependent manner (Gianoulakis, 1990). Increased β-E levels, in turn, activate μ and δ receptors and may play an important role in the reinforcing properties of alcohol intake. On the contrary, chronic exposure to alcohol leads to decreased β-E production that may be responsible for some feelings of discomfort and negative reinforcement (Gianoulakis, 2004). There are some reports indicating that chronic alcohol abuse results in lower concentration of β-E in the cerebrospinal fluid and plasma of alcoholics (Vescovi et al., 1992; Gianoulakis, 2004). Therefore, chronic alcohol abuse may lead to a central opioid deficiency due to decreased synthesis and release of β-E in the hypothalamus and pituitary as well as lower density and activity of the opioid receptors.

1.2. EXERCISE IN THE TREATMENT OF ALCOHOL USE DISORDERS

Low success rates (about 20%) (Madianos, 2003) and high relapse rates (ranging between 60 and 90%) (Brownell et al., 1986) are among the most significant problems facing the programmes for the treatment of alcohol detoxification. Alternative treatment methods have been used in order to combat this problem, including lifestyle modifications. One lifestyle modification that could be used as an adjunct method for alcohol abuse cessation and prevention of relapse in alcoholics but has not been sufficiently investigated is physical exercise (Donaghy & Mutrie, 1999; Donaghy et al., 1991; Read & Brown, 2003; Zschucke et al., 2012). Physical exercise can act as an alternative healthy activity versus addiction (Kosmidou et al., 2009). Recent reports indicate that pleasure ratings after exercise are higher compared to drinking alcohol in alcohol dependent patients (O'Brien et al., 2011). Moreover, physical exercise enhances mood and psychological wellbeing (Craft & Perna, 2004), improves health and wellness, can be cost-effective, flexible, and accessible, with minimal side effects compared to pharmacological treatment (Broocks et al., 1998).

Research on the use of exercise as an adjunctive strategy in treatment programmes of alcohol use disorders (AUDs) is limited. To author' knowledge, there are only seven studies in the literature that have investigated the effect of exercise on alcohol use related outcomes (Table 1). Acute exercise protocols were used in only one of those studies, while the other six studies involved medium- and long-term ET interventions with duration ranging from four to fifteen weeks. The small number of studies in combination with the limited parameters assessed lead to the conclusion that research on the efficacy of exercise in decreasing alcohol use is preliminary and the possible mechanisms involved have not been widely investigated yet. Nevertheless, it is interesting that most of the studies mentioned a positive effect of physical exercise in drinking patterns in their subjects,

rending physical exercise a promising tool for health practitioners in treatment programmes of AUDs.

Table 1: Studies on the effects of exercise on AUDs

Results	**Comments**
- No effects with regard to drinking episodes - Significant gains in cardiovascular fitness and self-cathexis scale -Significantly reduced sleep disturbances	- Small number of subjects - No other alcohol-related outcomes reported - No follow up data reported - Duration and type of control therapy not reported
- At 3-month follow up, significantly higher abstinence rates (self-report, validated by family members or colleagues) - Significant fitness gains	-Diagnoses and type of intervention not reported - Comparison of patients from different study centers receiving different treatments - No randomization
- Significant reduction in alcohol consumption in treatment groups - Alcohol consumption on weekdays affected - Significant fitness gains	- No clinical diagnosis of alcohol abuse or dependence
- No significant differences in abstinence rates - Significant improvements in power, fitness, body self-perception, and self-esteem after 15 weeks - Power and fitness gains maintained at 5-month follow up - No differences in body weight and resting pulse - Anxiety and depression equally reduced in both groups	- Diagnoses and type of therapy not reported - Unexplained high number of dropouts at 5-month follow up
- Significant lower scores for alcohol urges for EX vs CON between baseline and during exercise - No significant changes in alcohol urges scores for EX vs CON between baseline and immediately following exercise - No significant changes in any mood scores	- Small number of subjects - The ratings of alcohol urges tended to be higher at baseline for the moderate intensity in EX vs CON - Maybe participants had expectations for the effects of different experimental conditions on alcohol urges (expectation bias)
- Significantly higher rate of abstinent days at end of treatment and 3-month follow up - Significantly increased fitness and decreased BMI at end of treatment	- Small number of subjects - Lack of CON group (effects not explained by EX alone)
-Significant decrease in drinking days and heavy drinking days in AE. -Significantly lower alcohol and lower frequency of alcohol use compared to BA for those with sufficient attendance in AE ($\geq$8 exercise sessions) -Higher rate of abstinent days at 3-month follow up in AE - Non-significant difference in VO2max between conditions	- The CON group (BA) reported similar increases in exercise participation as the "experimental" group

Study	Subjects	Study design	Control group	Exercise intervention
Gary and Guthrie (1972)	20 alcohol-dependent patients (m)	- 4 weeks exercise intervention - Random assignment to EX or CON - Alcoholic treatment center	- Standard care - Group therapy, recreation programmes	- 4 weeks, 5 times/week or until 20 miles has been reached - Incremental running programme
Sinyor et al. (1982)	58 alcoholic patients (m,f)	- 6 weeks exercise intervention - Multicenter inpatient treatment programmes - Daily group therapy	- No exercise - Standard treatment followed	- 6 weeks, 5 times/week, 1hour each - Stretching, calisthenics, muscle-strengthening exercises, running or cross-country skiing
Murphy et al. (1986)	48 students, heavy social drinkers (m)	- 8 weeks exercise intervention - Randomized to CON 1, 2 and EX	- CON 1: standard intervention - CON 2: 3 times/week supervised meditation	- 8 weeks, 3 times/week, 30min each - Running at individual intensity
Donaghy (1997)	165 alcoholic patients (m,f)	- Multicenter study: inpatient and outpatient treatment programmes of different kinds and durations	- 3 weeks of supervised gentle stretching and breathing exercises, followed by 12 weeks of home-based training - 3 times/week, 30 min each	- 3 weeks of supervised exercise, followed by 12 weeks of home-based exercise - 3 times/week, 30min each - Aerobic and muscle-strengthening training
Ussher et al, (2004)	20 alcohol-dependent patients after detoxification (m,f)	- Counterbalanced cross-over study, inpatient treatment programme - Participation in the study following 10-14 days of alcohol detoxification - Randomized	- 10 minutes of light intensity cycling at 5-20% HRR	- 10 minutes of moderate intensity cycling at 40-60% of HRR
Brown et al. (2009)	19 alcohol-dependent patients after detoxification (m,f)	- Pilot study, outpatient alcohol programme (no details reported)	None	- 12 weeks,1/week supervised, 20–40 min each - Aerobic training (treadmill, ergometer) at 50–69% max HR - Including CBT-based exercise counseling, 2-3 times/week alone
Brown et al. (2014)	49 alcohol-dependent patients (m,f)	- Pilot study, outpatient alcohol programme, Aerobic exercise (AE)	Brief advice to exercise (BA)	- 12 weeks,1/week supervised, 20–40 min each - Aerobic training (treadmill, ergometer) at 50–69% max HR - Including CBT-based exercise counseling, 2-3 times/week alone

Abbreviations. m: male; f: female; EX: exercise; CON: control; CBT: Cognitive-Behavioral Therapy; MET: motivational enhancement therapy; CM: contingency management; HR: Heart Rate; BMI: Body Mass Index; HRR: Heart Rate Reserve.

1.3. RESEARCH SIGNIFICANCE

Taken all together, exercise could be an effective treatment for AUDs; however, more research is needed to understand the possible psychological and physiological mechanisms involved in the reduction of alcohol abuse through exercise. A theoretical framework that proposes a possible physiological mechanism that links exercise, β-E and alcohol cravings has been suggested by Zourbanos and his colleagues (2011), indicating that exercise could be used as an adjunctive strategy.

The purpose of this study was to investigate the effect of acute and long-term exercise on peptides of the HPA axis and other physiological parameters in individuals with AUDs. This is a first attempt to shed some light on how exercise influences physiological changes that could contribute to the improvement of alcohol related problems in humans.

1.4. RESEARCH HYPOTHESES

i) A bout of acute exercise of low intensity will increase blood β-E levels in alcoholics

ii) A bout of acute exercise of low intensity will reduce alcohol urge in alcoholics

iii) A bout of acute exercise of moderate intensity will increase blood β-E levels in heavy drinkers.

iv) A bout of acute exercise of moderate intensity will influence the levels of peptides of the HPA axis in heavy drinkers.

v) An 8-week ET intervention will reduce alcohol urge in heavy drinkers.

vi) An 8-week ET intervention will reduce alcohol consumption in heavy drinkers.

vii) An 8-week ET intervention will improve fitness, wellness and mood in heavy drinkers.

viii) An 8-week ET intervention will increase blood β-E levels in heavy drinkers.

ix) An 8-week ET intervention will influence the levels of peptides of the HPA axis in heavy drinkers.

1.5. STATISTICAL HYPOTHESES

Null hypotheses

i) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in β-E levels in alcoholics

ii) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in alcohol urge in alcoholics.

iii) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in β-E levels in heavy drinkers.

iv) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in the levels of peptides of the HPA axis in heavy drinkers.

v) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in alcohol urge before, during and after an 8-week ET intervention in heavy drinkers.

vi) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in alcohol intake before, during and after an 8-week ET intervention in heavy drinkers.

vii) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in β-E levels before, during and after an 8-week ET intervention in heavy drinkers.

viii) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in the levels of peptides of the HPA axis before, during and after an 8-week ET intervention in heavy drinkers.

Alternative hypotheses

i) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in β-E levels in alcoholics.

ii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in alcohol urge alcoholics.

iii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post-trial) in β-E levels in heavy drinkers.

iv) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in the levels of peptides of the HPA axis in heavy drinkers.

v) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in alcohol urge before, during and after an 8-week ET intervention in heavy drinkers.

vi) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in alcohol intake before, during and after an 8-week ET intervention in heavy drinkers.

vii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in β-E levels before, during and after an 8-week ET intervention in heavy drinkers.

viii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be no statistical significant differences in the levels of peptides of the HPA axis before, during and after an 8-week ET intervention in heavy drinkers.

1.6. RESEARCH LIMITATIONS

A limitation of the study is the small number of subjects due to practical difficulties in finding individuals that fulfill the requirements. Chronic heavy drinking often associates with co-morbidities meaning that in many cases physical exercise is contraindicated. In addition to that, many heavy drinkers believe that most people drink as much and as they do, thus they do not realize that they are facing a drinking problem and have a higher chance of developing AUDs.

Another limitation is the lack of a double-blind protocol for preventing bias (researcher and subjects were aware of which was the experimental protocol), the lack of control group in the 8-week ET intervention, and the lack of biochemical indices from other tissues than blood.

Unfortunately, direct measurement of changes in brain β-E involves cutting open the brain and employing radioimmunoassay techniques on brain slices. Indirect measurements of the levels of β-E and other endogenous opioids in the plasma may not reflect the levels of endogenous opioid levels in the brain; however, there are some speculations that the levels

of endogenous opioids in the plasma may act centrally and, therefore, reflect changes in central nervous system activity (Biddle & Mutrie, 1991).

2. LITERATURE REVIEW

2.1. DEFINITIONS RELATED TO ALCOHOL USE

Ethyl alcohol is a member of a class of organic compounds that are given the general name alcohols. Ethyl alcohol is the main type of alcohol in alcoholic beverages and is also called ethanol or simply alcohol. In this dissertation ethyl alcohol is referred to as alcohol.

2.1.1. STANDARD DRINK

The standard drink or unit measures the amount of alcohol in a drink. It is a simple and useful tool for information on how much a person drinks. Since different types of alcoholic beverages exist, a standard drink is expressed in grams of pure alcohol in order to make measurement as uniform as possible, meaning that a standard drink always contains a given amount of pure alcohol, regardless of the quantity or the type of alcoholic beverage. The definition of a standard drink may vary between countries, but generally it is defined to as 8-14 grams of pure alcohol.

The standard drink is usually expressed as a certain measure of beer, wine, or distilled spirits that does not necessarily correspond to the typical serving size of that alcoholic beverage in the country in which it is served. According to the WHO, one standard drink contains 10 grams of pure alcohol (WHO, 2010). Based on this and also knowing how much alcohol is contained in an alcoholic beverage (i.e. alcohol by volume, expressed as a percentage of total volume), the quantity of this alcoholic beverage that is equal to a standard drink can be calculated as follows:

1 Standard drink = [Amount of alcoholic beverage (litres)] x [Volume of alcohol (%)] x [density of alcohol at room temperature (0.789 g/ml)]

Table 2: Quantities of some popular alcoholic beverages in Greece, which are (approximately) equal to one standard drink.

Alcoholic beverage	% alcohol	ml of alcoholic beverage
Beer	5	250
Retsina	11	115
Wine	13	100
Ouzo, tsipouro	45	28
Whisky	40	32
Rum, vodka, gin	37	34

2.1.2. BLOOD ALCOHOL CONCENTRATION (BAC)

It is well understood that different doses of alcohol cause different behavioral and physiological responses. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the effects of alcohol consumption can include reduced inhibitions, slurred speech, motor impairment, confusion, memory problems, concentration problems, coma, breathing problems, death. Additionally, other risks of drinking can include car crashes and other accidents, risky behavior, violent behavior, suicide and homicide (NIAAA, 2013). However, different responses of individuals to the effects of alcohol are based on not only the quantity of alcohol consumed but also the mood, food, physiology (e.g. body composition, gender), physical health, medication, alcohol tolerance, drinking pattern, and family history. Consequently, the effects of alcohol consumption have been associated with the level of alcohol in blood, described by the term Blood Alcohol Concentration (BAC). BAC is usually expressed as a percentage of alcohol in the blood (g alcohol/dL). Table 3 summarizes the behavioral and physiological responses to different amounts of alcohol in the blood. BAC is used for legal or medical purposes, and can be conducted through a blood test. In Greece, the legal limit for driving is 0.05% BAC, meaning that there are 0.05 g of alcohol for every dL (100 mL) of blood. Responses to

different amounts of alcohol expressed as % BAC have been described indicatively (Bobick & Balaban, 1997) (Table 4).

Table 3: Responses to different amounts of alcohol in the blood, as measured by Blood Alcohol Concentration (BAC)

BAC (g/dL)	Stage	Observable Effects
0.01-0.03	Subclinical	• Behavior nearly normal by ordinary observation
0.03-0.09	Euphoria	• Sociable; talkative; increased self-confidence • Decreased inhibitions; diminution of attention; altered judgment • Beginning of sensory-motor impairment; loss of efficiency in finer performance tests
0.09-0.25	Excitement	• Emotional instability; loss of critical judgment • Impairment of perception, memory, and comprehension • Decreased sensory response; increased reaction time • Reduced visual acuity, peripheral vision, and glare recovery • Reduced sensory-motor coordination; impaired balance • Drowsiness
0.25-0.30	Confusion	• Disorientation; mental confusion and dizziness • Exaggerated emotional states • Disturbances of vision and of perception of color, form, motion, and dimensions • Increased pain threshold • Decreased muscular coordination; staggering gait; slurred speech • Apathy, lethargy
0.30-0.40	Stupor	• General inertial; approaching loss of motor functions • Markedly decreased response to stimuli • Lack of muscular coordination; inability to stand or walk • Vomiting; incontinence • Impaired consciousness; sleep or stupor
0.40-0.45	Coma	• Complete unconsciousness • Depressed or abolished reflexes • Subnormal body temperature • Impairment of circulation and respiration • Possible death
0.45-1.00	Death	• Death from respiratory arrest

Source: McGuire & Beerman, 2009

Table 4: Brief table of responses to different amounts of alcohol in the blood, as measured by Blood Alcohol Concentration (BAC)

BAC	Effect of drinks
0.02–0.03%	Changes in behavior, coordination, and ability to think clearly
0.05%	Sedation or tranquilized feeling
0.08–0.10%	Legal intoxication in many states
0.15–0.20%	Person is obviously intoxicated and may show signs of delirium
0.30–0.40%	Loss of consciousness
0.50%	Heart and respiration become so depressed that they cease to function and death follows

2.1.3. DRINKING PATTERNS

Drinking patterns describe not only the amounts of alcohol that a person consumes, but also the characteristics of that person, the drinking settings, and the drinking behaviour (International Center for Alcohol Policies [ICAP], 2014).

- **Abstinence from alcohol:** The WHO has noted that abstention is an important indicator of the impact of global alcohol consumption on health (WHO, 2011a). There are adults who have never consumed alcohol, adults who have previously consumed alcohol, but who have not done so in the previous 12-month period, and adults who have not had any alcoholic beverage in the past 12 months. Globally, it was estimated that abstention rates for men and women for the past 12 months in 2010 was 62%, while in Greece was 33.8% (WHO, 2014).
- **Moderate alcohol drinking:** It is defined as consumption that does not exceed approximately 3 standard drinks per day for men and 1.5 standard drinks per day for women; or consumption that does not exceed approximately 20 standard drinks per week for men and 10 standard drinks per week for women (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010). As it was referred previously, one standard drink contains 10 grams of pure alcohol (WHO, 2010). Many studies have shown

that this drinking pattern is beneficial for health; however, the definition of moderate alcohol drinking varies among studies and guidelines from different health organizations.

- **Binge drinking (or heavy episodic drinking):** a pattern of drinking occasionally at a level where there is a high risk of intoxication and acute consequences (WHO, 2004). According to the NIAAA, binge drinking is as a pattern of drinking that raises BAC levels to 0.08 g/dL (NIAAA, 2014). The WHO defines binge drinking as consumption of least 60 grams or more of pure alcohol on at least one occasion per month (WHO, 2010). Worldwide, about 7.5% of drinkers had at least one binge drinking event per month in 2010, while drinkers in Greece showed a much higher likelihood of binge drinking events per month (52.8%) (WHO, 2014). Binge drinking events may negate the benefits derived from light to moderate alcohol use (Poikolainen, 1998); however, this may be avoided when alcohol is combined with meals (Blanco-Colio et al., 2000; Trichopoulou et al., 2003; Stranges et al., 2004a).
- **Heavy drinking:** is a pattern of drinking that exceeds some standard of moderate drinking. Heavy drinking is often defined in terms of exceeding a certain daily (e.g. 3 standard drinks per day) or weekly volume (e.g. 20 standard drinks per day) or quantity per occasion (e.g. 4 standard drinks on an occasion, at least once per month). There is a high risk of acute or chronic health and social consequences in people with such persistent patterns of drinking (Puddey et al., 1999). Moreover, heavy drinkers have a higher risk of developing alcohol abuse or dependence than moderate alcohol drinkers. Other terms close to heavy drinking are habitual excessive drinking and harmful use (WHO, 2004).
- **Alcohol abuse:** is a drinking pattern that results in significant and recurrent adverse health and social consequences.
- **Alcohol dependence (or alcoholism):** uncontrollable alcohol use that is characterized by tolerance and withdrawal symptoms such as nausea, sweating, restlessness, irritability,

tremors, hallucinations and convulsions. Alcohol dependence is identified by using some internationally validated instruments, such as the Alcohol Use Disorders Identification Test (AUDIT; WHO, 2001), and diagnostic criteria, such as those found in the ICD-10 or DSM-IV (WHO, 2004). More detailed description of alcohol abuse and alcohol dependence is given in the following subtopic (2.1.4.).

More recently, the WHO (2011) has introduced another definition; the patterns of drinking score (PDS). PDS is an indicator of how people drink, on a scale of 1 (least risky drinking pattern) to 5 (most risky drinking pattern). According to the WHO, the PDS "reflects the alcohol-attributable burden of disease of a country, given the same level of alcohol consumption". It is estimated by taking into consideration the amount of alcohol consumed per occasion, festive drinking, the proportion of drinking when getting drunk, the proportion of drinkers who drink daily, drinking with meals, and drinking in public places. In Greece, the drinking pattern is thought to be somewhat risky (2 on a scale of 1-5) (WHO, 2014).

2.1.4. ALCOHOL USE DISORDERS

Alcohol use that exceeds the moderate upper limit can abolish beneficial effects or even cause negative health outcomes, and very often indicates harmful drinking patterns and alcoholism (WHO, 1980). According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association [APA], 1994), alcoholism is a broad term for problems with alcohol and it can be divided into two subcategories, alcohol abuse and alcohol dependence, which mainly differ in the severity of the condition.

Alcohol abuse is defined as a maladaptive pattern of alcohol use, leading to clinically significant impairment of distress, as manifested by at least one of the following symptoms, occurring within a 12-month period:

- Failure to fulfill family, work and other important obligations due to recurrent alcohol use
- Activities that may be hazardous to health due to recurrent alcohol use (e.g., car accidents)
- Recurrent legal problems due to alcohol abuse
- Recurrent alcohol use despite social or interpersonal problems due to the effects of alcohol abuse

However, the aforementioned symptoms never met criteria for alcohol dependence. Alcohol dependence is defined as a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following symptoms, occurring at any time in the same 12-month period:

- Continued use of the same amount of alcohol markedly diminishes its effect; or there is a need of markedly increased amounts of alcohol in order to achieve intoxication or desired effect
- The characteristic withdrawal syndrome for alcohol; or relieve/avoidance of withdrawal symptoms via alcohol (or a closely related substance) use
- Drinking larger amounts of alcohol or over a longer period than intended.
- Unable to control or cut down on drinking; or persistent desire
- Reduce or quit important social, occupational, or recreational activities due to alcohol drinking

- Spending a great deal of time to obtain, to use, or to recover from the effects of drinking
- Being aware of having a persistent or recurrent physical or psychological problem linked to alcohol but unable to quit drinking

Recently, the APA issued the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (2013), where the two DSM–IV disorders, alcohol abuse and alcohol dependence, merged into a broader one called "alcohol use disorders" (AUDs) with mild, moderate, and severe sub-classifications (American Psychiatric Association, 2013). Individuals must meet any two of the eleven criteria outlined in the DSM–5 during the same 12-month period in order to be diagnosed with an AUD:

- Sometimes ending up drinking more or longer than intended
- Failed to cut down or stop drinking more than once
- Spent a lot of time drinking or hangovering
- Having cravings or urge to drink
- Alcohol drinking (or being sick from drinking) often resulted in failing to fulfill family, work and other important obligations
- Continued to drink despite causing trouble with family or friends
- Given up or cut back on hobbies and other interesting activities in order to drink
- Exhibiting behaviours that increase the chances of getting hurt, while and after drinking
- Continued to drink despite resulting in a memory blackout, mental or other health problems

- Continued use of the same amount of alcohol markedly diminishes its effect; or there is a need of markedly increased amounts of alcohol in order to achieve intoxication or desired effect
- Withdrawal symptoms such as shakiness, irritability, depression, nausea, sweating, or illusions

Moreover, the WHO also uses the term AUDs as a group that comprises the diagnostic categories of alcohol abuse (also referred to as "harmful use of alcohol"), alcohol dependence (also referred to as "alcoholism"), and alcohol psychoses (WHO, 1992).

Another tool for the identification of AUDs is the AUDIT (WHO, 2001). AUDIT is widely used by health workers and researchers who encounter individuals with alcohol-related problems. AUDIT consists of 10 questions (scored individually from 0 = never to 4 = four or more times per week) about recent alcohol use, alcohol dependence symptoms, and alcohol-related problems (WHO, 2001). Scores between 8 and 15 indicate hazardous (or risky) drinking, which is a pattern of alcohol consumption that increases the risk of harmful consequences for the user or others (WHO, 1994). Scores between 16 and 19 suggest harmful drinking, which is a pattern of alcohol consumption that results in consequences to physical and mental health and maybe socials consequences (WHO, 1993; WHO, 1994). Scores of 20 or above indicate alcohol dependence and further diagnostic evaluation is required (WHO, 2001).

2.2. DOSE-RESPONSE ASSOCIATION

Many studies have documented that alcohol consumption is associated with the risk of certain diseases in a dose-response manner, which is often described by a J- or U-shaped distribution. That means that light to moderate alcohol use causes no negative effect on

health or even reduces the risk of several diseases (Kim et al., 2012; Brien et al., 2011; Baliunas et al., 2009) and mortality (Doll et al., 1994 check) while heavy drinking is harmful. However, individuals with risk factors for other diseases may not enjoy the beneficial effects of light to moderate alcohol use to the same extent as their healthy counterparts (Hozawa et al., 2010).

More detailed, a J-shaped association between alcohol consumption and the risk of combined type 2 diabetes mellitus (T2DM) and impaired fasting glycemia in men (Liu et al., 2010), as well as the risk of cardiovascular disease (CVD) (Di Castelnuovo et al., 2002; Corrao et al., 2004), especially stroke (Chiuve et al., 2008; Patra et al., 2010; Ronksley et al., 2011) in both men and women has been demonstrated. Also, a U-shaped association between alcohol consumption and the risk of T2DM (Hozawa et al., 2010; Baliunas et al., 2009; Nakanishi et al., 2003; Koppes et al., 2005; Carlsson et al., 2005) and CVD, such as sudden cardiac death (Chiuve et al., 2010) has been described.

Nevertheless, the first ascending leg of the U-shaped relation between alcohol consumption and the risk of disease may be observed when abstainers include individuals who quitted drinking due to health problems or individuals with other risk factors for disease (Marmot & Brunner, 1991). Moreover, a J- or U-shaped association between alcohol use and the risk of disease is not always present. For example, in a systematic review by Goldstein and his colleagues (2011), the association between alcohol consumption and hemorrhagic stroke was found to be linear (Ariesen et al., 2003; Feigin et al., 2005; Klatsky et al., 2002; Reynolds et al., 2003), but may vary with gender (Patra et al., 2010).

From the foregoing, it is apparent that the quantity of alcohol consumed plays an important role in the effects of alcohol in health; however, the drinking patterns must also be

considered. Drinking patterns have been linked to two main categories of disease outcome: injuries (both unintentional and intentional) and cardiovascular diseases.

2.3. EFFECTS OF ALCOHOL USE

Guidelines on alcohol use suggest that light to moderate consumption of alcohol can be beneficial for health. However, there is inconsistency regarding the definition of the dose among different international and national organizations. The Dietary Guidelines for Americans (5th edition) define as moderate alcohol consumption for healthy adult individuals up to 2.8 standard drinks (i.e. 28 grams of pure alcohol) per day (not to exceed 19.6 standard drinks per week) for men and up to 1.4 standard drinks (i.e. 14 grams of pure alcohol) per day (not to exceed 9.8 standard drinks per week) for women (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010).

The reason for lower dosage for women is their different physiology, absorption and metabolism of alcohol (lower activity of alcohol-degrading enzymes) compared to men (ICAP, 2003). Moreover, the recommended consumption of alcohol may be different for individuals meriting particular attention, such as pregnant women or alcoholics (ICAP, 2001).

Therefore, the effects of alcohol use on health outcomes may vary depending on many factors. Observational studies on alcohol consumption and the risk of disease highlight the beneficial effect of light to moderate alcohol use and the negative effect of heavy or binge drinking. However, there is inconsistency on the definitions of light, moderate and heavy alcohol use. Thus it is difficult to make recommendations for alcohol drinking for every occasion and only some general guidelines can be given.

2.3.1. POSITIVE EFFECTS OF ALCOHOL USE

2.3.1.1. CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide (WHO, 2008; WHO, 2011b). More than 17 million people die every year of CVD, and the most common are ischemic heart disease and cerebrovascular disease in both men and women (WHO, 2011b).

Atherosclerosis, the main cause of the most common fatal CVD, i.e. heart attack and stroke (WHO, 2011b), is a long and slow inflammatory pathological process in the walls of blood vessels. Therefore, changes in atherosclerotic factors such as lipid, thrombogenic and hemostatic factors, inflammatory markers and other molecules, may reduce the likelihood of developing CVD or delay its progression. Some of these biomarkers have been implicated in potential mechanisms by which moderate alcohol consumption reduces the risk of CVD (Brien et al., 2011; Huang et al., 2010; Imhof et al., 2008; Imhof et al., 2009; Pai et al., 2004; Mennen et al., 1999; Paassilta et al., 1998; Rimm et al., 1999; Zhang Q. H. et al., 2000; Wakabayashi, 2011; Rouillier et al., 2005). In a meta-analysis of randomized controlled trials moderate drinkers were found to have decreased serum levels of fibrinogen, a protein that promotes clot formation and increased levels of tissue type plasminogen activator that is implicated in clots clearance (Mennen et al., 1999). In addition to that, it has been shown that moderate drinkers exhibit lower levels of markers of inflammation and heart disease, such as C-reactive protein (CRP) compared with abstainers, suggesting that moderate alcohol consumption has anti-inflammatory properties (Albert et al., 2003; Stewart et al., 2002; Imhof et al., 2001).

2.3.1.2. TYPE 2 DIABETES MELLITUS

A number of studies suggest that light to moderate alcohol consumption is associated with decreased risk of T2DM (Conigrave et al., 2001; Nakanishi et al., 2003). The underlying mechanism for this association is not yet clearly understood; however, the improvement in insulin sensitivity is thought to be involved (Crandall et al., 2009; Hendriks, 2007; Davies et al., 2002; Lazarus et al., 1997; Facchini et al., 1994). This suggested mechanism is based on the observation that moderate drinking lead to higher levels of adiponectin (Pischon et al., 2005; Beulens et al., 2007). Adiponectin levels may positively associate with insulin sensitivity, while higher adiponectin levels are associated with lower risk of T2DM (Li et al., 2009).

Moreover, markers of inflammation and endothelial dysfunction are positively associated with the risk of T2DM (Hu et al., 2004; Meigs et al., 2004), while moderate alcohol use is thought to lower the levels of such markers (Imhof et al., 2001; Sierksma et al., 2002). Finally, since light to moderate alcohol consumption (up to 30 g/d alcohol) has not been shown to induce weight gain in women (Wannamethee et al., 2004) and body mass index (BMI) is the most important predictor of T2DM, especially in women (Hu et al., 2001), it is suggested that light to moderate alcohol use is not a causative factor of T2DM.

2.3.1.3. OTHER CONDITIONS

A number of studies have found that light to moderate alcohol use reduces the risk of developing gallstones (Maclure et al., 1989; Attili et al., 1998; Halldestam et al., 2009; Walcher et al., 2010). It has been shown that frequent alcohol consumption of any given amount (5-7 days/ week) may result in lower gallstone occurrence risk than abstinence from alcohol drinking. Alcohol drinking is also related to the formation of kidney stones.

Consumption of approximately 240ml wine daily has been found to decrease the risk of kidney stones by 59% (Curhan et al., 1998). Additionally, moderate alcohol consumption is associated with higher bone mineral density and lower osteoporosis rates in postmenopausal women (Siris et al., 2001).

2.3.1.4. SUBSTANCES IN ALCOHOL THAT CONTRIBUTE TO HEALTH BENEFITS

Many studies have shown that regular light to moderate alcohol use can cause the above mentioned protective effects. However, it is not clear which types and constituents of alcoholic beverages are more beneficial. Research has focused on alcohol and polyphenol content of alcoholic beverages, in order to explain the dose-response association of the consumption of several alcoholic beverages and disease risk.

Except for alcohol, certain alcoholic beverages have some other constituents that may provide additional benefits, such as prevention of oxidative damage and free radical formation. For instance, red wine has gained greater interest from the scientific community in comparison to white wine because of its greater content in polyphenols. Resveratrol, a natural phenol that is mainly found in red wine, may promote human health in a dose-dependent manner. There is some evidence that resveratrol provides cardioprotection and maintains a stable redox environment, while it may also have pro-apoptotic and anti-carcinogenic properties (Mukherjee et al., 2010). However, there is controversy about whether polyphenols or alcohol is the most effective component of alcoholic beverages in terms of health benefits (Rimm, 1996).

2.3.2. NEGATIVE EFFECTS OF ALCOHOL USE

Excessive alcohol consumption can negatively affect both mental and physical health (Caan & Belleroche, 2002). Harmful alcohol use accounts for about 4.5% of all diseases and injuries worldwide (WHO, 2011a), such as liver cirrhosis, epilepsy, several types of cancer, violence, road traffic accidents and poisoning (WHO, 2011a), while it also increases impulsivity and antisocial behaviour (Lejuez et al., 2010). The quantity of alcohol consumed and the drinking pattern seem to be major determinants of disease and injury. Moreover, alcohol abuse is a significant cause of death (WHO, 2011a). About 2.5 million deaths worldwide are attributable to alcohol every year, meaning that about 4% of all-cause mortality worldwide is caused by alcohol (WHO, 2011a).

2.3.2.1. REDOX STATUS

Oxidative stress is an imbalance between oxidants and antioxidants in favor of the oxidants (Sies & Jones, 2007). Oxidative stress can cause damage in biological molecules (lipids, proteins and DNA) and is responsible for the development of several diseases. Alcohol is among those factors that can lead to impaired redox status (Das & Vasudevan, 2007). Chronic heavy alcohol intake has been reported to increase the production of reactive oxygen species (ROS) and to impair antioxidant defense mechanisms (Zima & Kalousova, 2005). Thus alcohol-induced oxidative stress has been associated with the pathogenesis of alcohol-related diseases, such as alcohol liver disease, alcoholic cardiomyopathy and cancer (Lieber, 1994; Tsukamoto, 2001; Lumeng & Crabb, 2001; Arteel et al., 2003; Zima & Kalousova, 2005).

2.3.2.2. NERVOUS SYSTEM

Chronic excessive alcohol consumption may distort brain chemistry and neurological function, and may lead to medical conditions such as impaired brain development, brain shrinkage, dementia, physical dependence, neuropsychiatric and cognitive disorders (Panza et al., 2008). One possible factor that increases the risk of these conditions in alcoholics may be increased levels of homocysteine, which have been found to enhance the vulnerability of neuronal cells to excitotoxic and oxidative injury in vitro and in vivo. This in turn negatively affects volume in the hippocampus, which is involved in memory functions (Bleich et al., 2003). Alterations in brain chemistry can also induce chronic fatigue, a condition that incapacitates a person to complete tasks at normal performance (Avellaneda Fernández et al., 2009). Synaptic plasticity and neuronal connectivity are developed in adolescence and exposure to alcohol at this stage of life can result in cognitive deficits (Guerri & Pascual, 2010).

Acetaldehyde, a substance produced by the liver during the breakdown of alcohol, has been thought to increase the risk of Alzheimer disease (Ohta et al., 2004). Moreover, thiamine deficiency, which is common among heavy drinkers, causes severe brain dysfunctions. Chronic thiamine deficiency leads to the Wernicke- Korsakoff syndrome, characterized by ataxia and impaired memory (Butters, 1981). Alcoholism is also associated with brain structures, like amygdala and hippocampus, which are involved in emotional and memory processing (Marinkovic et al., 2009). This could explain why psychiatric disorders like psychosis, depression and anxiety disorder are commonly seen among heavy drinkers. However, the causative relationship between alcohol abuse and psychiatric disorders is not very clear (Fergusson et al., 2009). Additional mechanisms responsible for cognitive dysfunction are neuroinflammation, reduced neurogenesis and inhibited signaling pathways (Pascual et al, 2009; Taffe et al., 2010).

2.3.2.3. CHRONIC METABOLIC DISEASES

It has been observed that increasing alcohol consumption is associated with increasing number of conditions that predispose to chronic metabolic disease (Bradley et al., 1998). It is has been shown that there is a dose-response relationship between alcohol consumption and the odds ratio for the development of metabolic syndrome (Yoon et al., 2004). Moreover, a J-shaped relationship between consumption of alcohol and CVD exists; although there is a protective effect of light to moderate alcohol consumption in individuals with increased risk of coronary heart disease, epidemiological data suggest that heavy alcohol consumption has the opposite results (Di Castelnuovo et al., 2009; Klatsky, 2009). Excessive alcohol consumption may lead to an increased risk of heart failure, stroke, and cardiomyopathy, which induces heart muscle impaired contraction and can lead to congestive heart failure. The main mechanism suggested is through increased levels of acetaldehyde, which impede cardiac muscle homeostasis (Saremi et al., 2008). Even though women may be more susceptible to alcoholic cardiomyopathy, the condition is more common among men (Urbano-Marquez et al. 1995).

Moderate alcohol drinkers may have a lower risk of diabetes than abstainers; however, binge drinking and generally heavy alcohol consumption may increase the risk of type 2 diabetes in women (Carlsson et al., 2003) through interference with insulin sensitivity regulation (Hong et al., 2009).

2.3.2.4. GASTROINTENSTINAL SYSTEM

Chronic alcohol abuse is the most common cause of liver disorders such as alcoholic fatty liver, alcoholic hepatitis and cirrhosis (O'Shea et al., 2010). Most of the alcohol consumed (about 80%) is metabolized in the liver and, therefore, alcohol misuse often leads to liver

damage. Metabolism of large quantities of alcohol results in the secretion of pro-inflammatory cytokines (TNF-alpha, IL6 and IL8), oxidative stress, lipid peroxidation, and acetaldehyde, which in turn cause inflammation, apoptosis and finally fibrosis of the liver (Longstreth, 2009). These adverse effects can be reversed with alcohol use cessation in cases of mild alcohol misuse. Unfortunately, in cases of severe liver disease, treatment may involve a liver transplant in alcohol abstinent patients. Alcohol misuse is also a very common cause of both acute and chronic pancreatitis, and pancreatic cancer (Frossard et al., 2008; Bachmann et al., 2008).

2.3.2.5. OTHER CONDITIONS

Alcohol has been classified as a known carcinogen by the International Agency for Research on Cancer, the specialized cancer agency of the WHO (Cogliano et al., 2011). A 2011 study showed that one in 10 of all cancers in men, and one in 33 in women, were attributable to past or current alcohol consumption (Schütze, 2011). The most convincing evidence exists for cancers of the oral cavity, pharynx and larynx, oesophagus, colorectum in men, and breast (pre- and post-menopause) in women (Andréasson & Allebeck, 2006). A possible mechanism is that high levels of acetaldehyde, produced after alcohol consumption, induce DNA damage of healthy cells (Ohta et al., 2004). Alcohol is the main cause of liver cancer in the Western world, accounting for 32-45% of hepatic cancers (Voigt, 2005).

Additionally, excessive alcohol intake can negatively affect reproductive health. Alcohol can cause increased levels of estrogens, which can lead in feminization of males and may increase the risk of breast cancer in women (Gavaler, 1998). Some other negative effects

of alcohol abuse are excess bone loss, myopathies and a range of skin disorders (Peer & Newsham, 2005; Kostović & Lipozencić, 2004).

2.4. OPIOID SYSTEM

The endogenous opioid system consists of three major classes of endogenous opioid peptides, endorphins (α-endorphin, β-endorphin, γ-endorphin, α-neo-endorphin, and β-neo-endorphin), enkephalins (met-enkephalin and leu-enkephalin), and dynorphins, that derive from distinct precursor proteins, pro-opiomelanocortin (POMC), pro-enkephalin and pro-dynorphin, respectively.

Opioid peptides act as neurotransmitters and neuromodulators at three classes of receptors, designated μ, δ, and κ. Endorphins bind to μ, and δ receptors with comparable affinity (Branson & Gross, 2001). Enkephalins mainly interact with the δ receptor and dynorphins with the κ receptor (Koneru et al., 2009).

Opioid peptides and their receptors are widely and selectively distributed in the central and peripheral nervous systems, particularly in circuits involved in modulation of pain, reward and reinforcement, responses to stress, thermoregulation and substrate metabolism (Fatouros et al., 1995; Fatouros et al., 1997; Goldfarb & Jamurtas, 1997; Jamurtas et al., 2000; Gianoulakis, 2001; Jamurtas et al., 2001; Jamurtas & Fatouros, 2004; Jamurtas et al., 2011). Thus the opioid system has an important role in mechanisms of analgesia, reward-mediating food intake and drug addiction, and modulation of emotion and stress responses. Opioid and opiate drugs are usually used for their euphoric and/or analgesic effects. These drugs act at these same receptors with endogenous opioids and produce both analgesia and undesirable side effects.

Pro-opiomelanocortin (POMC), one of the three precursors of the endogenous opioid peptides, is cleaved into smaller proteins such as β-E, adrenocorticotropin (ACTH), and others (Gianoulakis, 2001). β-E is a multi-functional peptide hormone that is the most representative of the endogenous opioid system (Gianoulakis, 2001). β-E is mainly synthesized and stored in the anterior pituitary gland (Guillemin et al., 1977); however, there is some evidence indicating that it can also be synthesized in immune system cells (Stein, 1995; Jessop, 1998; Mousa et al, 2004). β-E can reduce perception of pain due to its analgesic effects. Moreover, β-E levels increase during exercise and are associated with a sense of well-being or euphoria experienced by the trainee during and after exercise (Farrell et al., 1987; Goldfarb et al., 1990).

2.5. ALCOHOL USE DISORDERS

The development of alcohol abuse and dependence may be influence by genetic and environmental factors (Enoch, 2006); however, the exact mechanisms involved are not fully understood. Some factors that are thought to influence the occurrence of alcohol dependence include mental health, stress, social environment, family history, age and ethnicity (Agarwal-Kozlowski & Agarwal, 2000; Chen et al., 2009).

2.5.1. PHYSIOLOGICAL CAUSES OF ALCOHOL USE DISORDERS

2.5.1.1. ALCOHOL'S EFFECT ON DIFFERENT REGIONS OF THE BRAIN

Heavy drinkers are at risk of developing alcohol addiction; however, many of them abuse alcohol over a long period of time without becoming addicted to alcohol (Vaillant, 2003). Pathophysiology of alcohol abuse is very complicated and remains largely obscure, and the

exact physiological mechanism by which heavy drinkers develop alcohol addiction is not known yet. Alcohol does not have a specific neurotransmitter binding site in the brain, unlike most illicit drugs of abuse. Thus research is more focused on the investigation of the effects of alcohol on pathways of neuronal communication that integrate the activities of multiple brain regions.

A pathway in the brain that is thought to play a central role in the development of alcohol dependence is the mesolimbic dopamine system (MDS). MDS is the most important reward pathway in the brain that carries dopamine from one area of the brain to another. MDS is the projection of ventral tegmental area (VTA) that mainly corresponds to the nucleus accumbens (NAc). VTA is a part of the midbrain that consists of dopaminergic, GABAergic, and glutamatergic neurons (Pierce & Kumaresan, 2006). The NAc is found in the ventral striatum and is composed of medium spiny neurons (Zhang T. A. et al., 2006; Purves et al., 2008), which receive input from the dopaminergic neurons of the VTA and the glutamatergic neurons of the hippocampus, amygdala, and medial prefrontal cortex. All these regions are involved in both behaviour changes and the process of alcohol dependence (Kalivas & Volkow, 2005). Thus changes in the MDS caused by alcohol abuse result in rewarding and addictive effects.

2.5.1.2. REINFORCEMENT AND NEUROADAPTATION

Reinforcement and neuroadaptation are processes that contribute to the development of alcohol addiction. Positive reinforcement occurs when a rewarding stimulus (e.g. alcohol) leads to a behaviour response. Negative reinforcement occurs when the removal of an aversive stimulus (relief of an unpleasant state) leads to a behaviour response. Neuroadaptation is a term that describes compensatory adjustments by which the brain

continues performing its normal functions despite the presence of alcohol (Higley et al., 2012). Neuroadaptation includes the process of sensitization, tolerance and physical withdrawal (Koob, 2003; Gilpin & Koob, 2008). Reinforcement and neuroadaptation may be responsible for both acute and chronic responses to alcohol. In addition to that, some neuroadaptive changes may be permanent and lead to relapse long after alcohol intake cessation (Koob et al., 1992).

2.5.1.3. ALCOHOL REINFORCEMENT AND CHANGES IN BRAIN PATHWAYS

Genetic predisposition, adverse life experience or both are factors that can increase a person's chance of developing alcohol dependence by affecting brain function. Adverse life experience can lead to chronic release of stress hormones resulting in persistent negative emotional state (e.g., fear, anger, guilt or shame) or anxiety, distress, irritability, sadness and poor affect regulation. Intermittent, repeated exposure to alcohol results in sensitization of the brain reward system (Robinson & Berridge, 1993) so that alcohol use and behaviours linked to changes in the MDS may induce more powerful and intense feelings of euphoria and pleasure. This could explain why some individuals use alcohol in order to reduce emotional distress (Goodman, 2009).

2.5.1.4. ALCOHOL MODIFIES COMMUNICATION BETWEEN NEURONS

Chemical synapses are specialized junctions that allow neurons to signal each other. Alcohol can affect synaptic transmission and modify communication between neurons in the brain.

Alcohol affects the brain's neurons by altering neuron membranes, ion channels, enzymes, and receptors. Chronic exposure to alcohol can lead to brain adaptations and the

development of alcohol tolerance. Alcohol binds directly to certain neurotransmitter receptors and inhibits their function. This inhibition of the neurotransmission occurs in two ways: (1) alcohol inhibits the excitatory channels on the postsynaptic neuron; (2) alcohol lowers the rate of action potentials from the presynaptic neuron. As a result, neuron cells may increase the number of receptors or alter the molecular composition of receptors or cell membranes in order to compensate inhibition of receptor function by alcohol.

The receptors that can be affected by alcohol are those for the neurotransmitters acetylcholine (ACh), serotonin or 5-hydroxytryptamine (5-HT), gamma aminobutyric acid (GABA), and glutamate. Some studies have shown that alcohol lowers the excitatory actions of glutamate at the N-methyl-D-aspartate (NMDA) receptor (a subtype of glutamate receptor), and enhances the inhibitory actions of GABA at the $GABA_A$ receptor (Diamond & Gordon, 1997). These two actions contribute to the reduction of the pace of brain activity and may also explain to some extend the claim that alcohol acts as a depressant.

Furthermore, dopamine, serotonin, and opioid peptides interact with their receptors in order to modulate the activity of neurons. Dopamine release in the nucleus accumbens after alcohol administration is linked with the development of alcohol addiction (Rassnick et al., 1992; Brodie et al., 1999). Serotonin may also increase dopaminergic activity in the nucleus accumbens contributing to rewarding effects of alcohol. Moreover, serotonin may be involved in alcohol tolerance, withdrawal and intoxication (Valenzuela, 1997). Opioid peptides may also increase the rewarding effects of alcohol (Roberts et al., 2000).

2.5.1.5. ALCOHOL AND OPIOID SYSTEM

It has been suggested that alcohol use is associated with the activation of the endogenous opioid system (Gianoulakis, 2001, 2004). Research findings indicate that acute or light alcohol intake stimulates the release of opioid peptides in brain regions associated with reward and reinforcement and they partly mediate the reinforcing effects of alcohol. Moreover, growing evidence indicates that the endogenous opioid system may be involved in the development and maintenance of AUDs. Chronic heavy alcohol use results in a central opioid deficiency, which may be perceived as opioid withdrawal. As a result, a greater alcohol intake is promoted through negative reinforcement (Gianoulakis, 2001).

Some individuals have a genetic predisposition to alcohol dependence. Genetic factors that may increase the β-E response to alcohol (Oswald & Wand, 2004), and dysfunctions in the activity of several neurotransmitter systems, may influence alcohol dependence. Several physiological functions that can be altered by specific genetic activity have been found. For example, genes encoding enzymes that metabolize alcohol also influence the risk of AUDs (Hurley et al., 2012). However, specific genes that can modulate alcohol use have not been identified yet.

2.5.2. TREATMENT/MANAGEMENT OF ALCOHOL USE DISORDERS

There are various approaches to the treatment of AUDs. The treatment approach is chosen mainly on the basis of severity of the problem being addressed. Some individuals may require only minor behavioural modifications to address emerging problems; however, more intensive secondary and tertiary prevention may be needed for heavy drinkers experiencing social or health problems (ICAP, 2011). Treatment usually includes three stages: detoxification, rehabilitation, and maintenance.

Treatment approaches to alcoholism may involve behaviour modifications, psychological support, support groups, and pharmacological treatment. A treatment approach widely used for more than a decade and applies to both patients with very serious problems and individuals with less severe alcohol problems, is motivational interviewing (Miller & Rollnick, 2002). This approach helps the patient to increase intrinsic motivation and commitment to treatment, thus enhancing motivation to change.

Some approaches may aim at alcohol abstinence while some other approaches may aim at changing the drinking pattern to one that is moderate and compatible with a healthy and balanced lifestyle (ICAP, 2011). The more effective and suitable approach for a particular individual should be determined on a case-by-case basis (Kadden et al., 2003; Longabaugh & Wirtz, 2001, 2003).

Physical exercise has been proposed as an alternative approach to the treatment of alcohol use disorders (Donaghy & Mutrie, 1999; Donaghy et al., 1991; Read & Brown, 2003; Zschucke et al., 2012). Physical activity can act as an alternative healthy activity to addiction and is available to people who may not have access to other forms of treatment such as psychological intervention or medication. However, treatment involving physical activity requires the active participation and commitment of the individual. Thus it has been shown that when the person is let free to choose the type and intensity of exercise that is bound to follow, the treatment is more effective (Ekkekakis, 2009). The appropriate type and intensity of exercise for mood improvement and alcohol intake reduction has not been found yet and depends on many factors (Ekkekakis & Acevedo, 2006).

2.6. EXERCISE FOR THE TREATMENT OF ALCOHOL USE DISORDERS

Physical exercise has been proposed as an adjunctive strategy in treatment programmes for

AUDs. However, research on the effect of ET interventions on alcohol intake in individuals with AUDs is scarce. To the authors' knowledge only seven studies have investigated the effect of exercise on alcohol use and related outcomes (Table 1). The results of these studies are controversial; however, most of these lead to the conclusion that exercise may be a promising strategy for addressing AUDs.

Gary and Guthrie (1972) investigated the effects of a 4-week jogging programme on alcohol consumption and self-esteem in alcoholic patients. The results showed that there was no difference in alcohol drinking episodes after intervention, although improvements in self-esteem and fitness were observed.

In a study by Sinyor and colleagues (1982), the effect of a 6-week fitness programme in fifty-eight individuals who were receiving treatment for alcohol dependence was studied. The results showed that participants had significantly higher abstinence rates and fitness gains after 3 and 18 months of follow up than control group. However, there were a number of methodological limitations in this study, with the most important being that the control group was consisted of patients from different therapy centers receiving several treatments. Therefore, the results from this study must be interpreted carefully.

A study by Murphy and colleagues (1986) investigated the effects of exercise and meditation on alcohol consumption in sixty college students who were heavy social drinkers. Subjects were randomly assigned to three groups: (1) a no-treatment control group (CON), (2) an experimental group which involved participation in an 8-week ET intervention (ET), and (2) another group which involved participation in meditation training (MT). All subjects self-recorded their daily ET programme and alcohol consumption throughout the study. The results showed significantly reduced alcohol consumption during intervention in the treatment groups (ET and MT) compared to CON. Moreover, participants in ET were reported to have gained fitness during intervention and

after 6 weeks of follow up. These results indicate that drinking behaviour may correlate with alcohol consumption but not with fitness gains. Several physiological, psychological, and social mechanisms activated by exercise have been suggested to positively affect individuals with AUDs (Read & Brown, 2003). This study by Murphy reinforces the hypothesis that since dopaminergic reinforcement mechanisms in the neural system are activated by both exercise and alcohol, exercise produces similar pleasurable effects with alcohol consumption (Cronan & Howley, 1974; Thoren et al., 1990).

Donaghy (1997) investigated the effects of a 3-week supervised ET programme followed by a 12-week home based ET programme in 165 adults in an alcohol treatment programme. Subjects were randomly assigned to two groups; the experimental group which included muscle stretching and aerobic exercise (supervised for 3 weeks and then home based for another 12 weeks), and the control group which included gentle stretching and breathing exercise (supervised for 3 weeks and then home based for another 12 weeks) 3 times per week. The results showed that there were no differences in flexibility, body weight and resting pulse between the two groups. However, there was a significant higher improvement in fitness and power after the ET programme in the experimental group, and these improvements were maintained after 5 months of follow up. No differences in abstinence and relapse rates were found between the two groups, while symptoms of anxiety and depression were equally reduced in both groups. Throughout the intervention and a 5-month follow up, a high number of dropouts occurred in both groups. These results indicate that a 3-week supervised ET programme may not induce significant changes in rates of abstinence, relapse, depression and anxiety, despite improvement in fitness.

Ussher and colleagues (2004) conducted a counterbalanced cross-over study to investigate the effect of a brief bout of moderate intensity exercise on alcohol urges and mood disturbance in twenty alcohol dependent individuals. All subjects participated in the study

after completion of a 3-month detoxification programme, during which they abstained from alcohol. Subjects underwent two conditions in a counterbalanced order: (1) 10 min of moderate intensity exercise (experimental condition), and (2) 10 min of light intensity exercise (control condition). No difference in mood between groups was shown throughout the study. Alcohol urges were non-significantly higher in the experimental than control condition at the baseline. The results showed that subjects in the experimental condition reported significantly reduced alcohol urges compared with control condition only during exercise. Alcohol urges did not differ between groups immediately after exercise, as well as 5 and 10 minutes after exercise. Therefore, exercise of moderate intensity and short duration may provide some short-term relief from alcohol urges during exercise but may not be capable of influencing β-E, which is thought to link alcohol urges with exercise. This is the first and only investigation of the acute effects of exercise on alcohol urges.

Brown et al. (2009) investigated whether a 12-week aerobic ET programme of moderate intensity can be used as an adjunctive intervention for alcohol dependent patients in recovery. Nineteen patients receiving ongoing addiction treatment for alcohol dependence participated in the programme. All participants reported their last drink 0 to 58 days before intervention (mean = 19.4 days). Preliminary results showed a significant higher rate of abstinence days at the end of the programme and after 3 months of follow up; however, there was no control condition. Moreover, there was a significant increase in fitness and decrease in BMI at the end of treatment; however, there was no difference after 3 months of follow up.

More recently, Brown and his colleagues (2014) investigated again the effects of a 12-week aerobic ET programme of moderate intensity on alcohol use related outcomes using a larger sample size. Forty nine alcoholic patients were assigned in one of the following groups: (1) a 12-week aerobic ET programme (50-69% of the MHR) (experimental group)

or (2) brief exercise advices (control group). The results showed that the ET programme led to a significant reduction in alcohol drinking days and heavy drinking days in the experimental group. Moreover, participants with sufficient exercise attendance (at least 8 exercise sessions) reported significantly lower amount and frequency of alcohol use compared to the control group. After a 3-month follow up period, it was reported that participants in the experimental group had higher rate of abstinent days, while adherent participants in the control group had significantly greater heavy drinking days during this period.

In conclusion, research on the effects of exercise on individuals with AUDs is limited. The type and intensity of exercise are associated with a euphoric feeling during and after exercise (Farrell et al., 1987; Goldfarb et al., 1990) and may influence the desire for alcohol consumption. The duration of exercise that affects the desire for alcohol consumption is questionable. Since human studies are scarce, responsible mechanisms for this effect of exercise on alcohol consumption are still unclear.

2.6.1. MECHANISMS OF EXERCISE EFFECTS ON ALCOHOL ABSTINENCE

Physical activity is an effective means of preventing and reducing the risk of many diseases, and improving overall health and wellness. It has been suggested that exercise has a beneficial role in the treatment of addictions. Exercise may attenuate the negative effects of alcohol consumption on blood coagulation, fibrinolysis and platelets, and also may attenuate the alcohol-induced decline in hepatic mitochondria and oxidative damage (El-Sayed et al., 2005). Furthermore, accumulating evidence suggests that exercise may directly affect mechanisms of alcohol addiction (Gianoulakis, 2001, 2004; Oswald and Wand, 2004). These mechanisms are mainly psychological and physiological. In regards to

mental health, exercise has many beneficial effects on mood, anxiety, depression, self-perception and self-efficacy (Hughes, 1984; Ekkekakis & Petruzzello, 1999; Read & Brown, 2003). For all these reasons, exercise has been proposed and used as an adjunctive strategy in the treatment of substance dependence (Read & Brown, 2003). However, studies on the possible psychological, physiological and biochemical mechanisms activated by exercise and are involved in the reduction of harmful alcohol consumption are scarce or non-existent.

2.6.1.1. PSYCHOLOGICAL MECHANISMS

Social cognitive theory refers to a psychological model of behaviour that emerged primarily by Bandura (1977). The central concept of this theory is self-efficacy, which is the belief that a person has the ability to succeed in a particular situation. Thus engagement of a person in an ET programme leads to increased self-confidence, self-esteem and self-efficacy levels of that person (Landers & Arent, 2001; Paluska & Schwenk, 2000). This process could be used in strategies for alcohol abstinence.

A psychosocial mechanism that may be involved in alcohol abuse is the use of alcohol to cope with stress of everyday life. Exercise is a means of stress reduction and, therefore, may be used to reduce alcohol urge (Monti et al., 1995). Another psychosocial mechanism through which alcohol abuse could be reduced is social interaction. During exercise, social interaction can create strong relationships among people participating in it, which in turn may have a positive impact on mental health (North et al., 1990). Physical activity may help improve social support network, and it may also be an acceptable form of social support in alcohol-dependent individuals under rehabilitation (Longabaugh et al., 1998).

It is common for persons with AUDs to consume alcohol in order to relieve symptoms of depression. On the other hand, alcohol abuse increases the risk of depression by affecting the chemistry of the brain. The beneficial effects of physical activity on mood (Faulkner & Biddle, 2001), depression (O'Neal et al., 2000) and anxiety (O'Connor et al., 2000) are well documented. Walking programmes have shown to have a positive impact on depression symptoms in people suffering from moderate to severe depression (Mobily et al., 1996; Faulkner & Biddle, 2004). Therefore, physical activity may function as a strategy for coping with AUDs.

In conclusion, development a physically active lifestyle may lead to improved health, quality of life and may also be an alternative form of behaviour to AUDs.

2.6.1.2. PHYSIOLOGICAL MECHANISMS

A possible physiological mechanism is based on the association of exercise and alcohol cravings with the endogenous opioid system. The endogenous opioid system is mainly involved in the modulation of the response to pain, reward and reinforcement, and also in homeostatic adaptive functions, such as thermoregulation and energy intake (Olson et al., 1990). There is some evidence suggesting that physical activity influences β-E secretion by the anterior pituitary gland and the hypothalamus. B-E levels increase during exercise (Goldfarb et al., 1987), are influenced by the intensity and duration of exercise (Farrell et al., 1987; Goldfarb et al., 1990, 1991) and are associated with a feeling of euphoria by the trainee during exercise. Moreover, β-E levels may be involved in the metabolism of carbohydrates both during rest (Fatouros et al., 1995) and exercise conditions (Fatouros et al., 1997; Goldfarb & Jamurtas, 1997; Jamurtas et al., 2000; Jamurtas et al., 2001;

Jamurtas & Fatouros, 2004; Jamurtas et al., 2011) due to the fact that its receptors are present in many parts of the body which participate in the metabolism of substances.

The endogenous opioids are thought to be participating in the phenomena of tolerance to alcohol and abstinence from it. It is known that alcohol consumption increases β-E levels and leads to elevated euphoria (Gianoulakis, 2004). It has been also reported that β-E levels are decreased in the initial phase of alcohol abstinence (Inder et al., 1998), and that there is a central deficiency of β-E and significantly increased levels of ACTH in the cerebrospinal liquid of alcoholics (Genazzani et al., 1982). These findings suggest that there may be significant changes in peptides related to POMC in alcoholics.

Moreover, genetic factors may contribute to the development of alcoholism. B-E levels have been found to be lower in children of alcoholics than in normal individuals, and these levels were found to be even more reduced when both parents were alcoholics (Del Arbol et al., 2007).

Both amount and frequency of alcohol consumption are thought to affect the endogenous opioid system. Acute or light alcohol consumption results in greater β-E levels; however, chronic heavy alcohol use induces adaptive changes in several neuronal systems in order to maintain their functional activity at normal levels, resulting in central opioid deficiency in the absence of alcohol (Gianoulakis, 2004). Thus abstinence from alcohol in individuals with AUDs has been associated with decreased β-E levels, which may result in alcohol withdrawal and promote further alcohol consumption (Gianoulakis, 2004; Inder et al., 1998).

A model of the possible relationship between alcohol urge, β-E levels and physical exercise has been suggested by Zourbanos and his colleagues (2011) (Figure 1). This model is based on the assumption that since both alcohol consumption and physical

exercise increase β-E levels in hypothalamic and peripheral level, alcohol consumption and physical exercise affect and are affected by the opioid system. As mentioned before, alcoholics have decreased secretory capacity of β-E and, therefore, increased levels of alcohol urge (Esel et al., 2001), which in turn increases the β-E secretion (Gianoulakis, 2004). Considering any suitable volume of physical exercise can potentially lead to increased β-E levels (Goldfarb et al., 1990), it can be hypothesized that exercise may substitute alcohol consumption and/or decrease the desire for it.

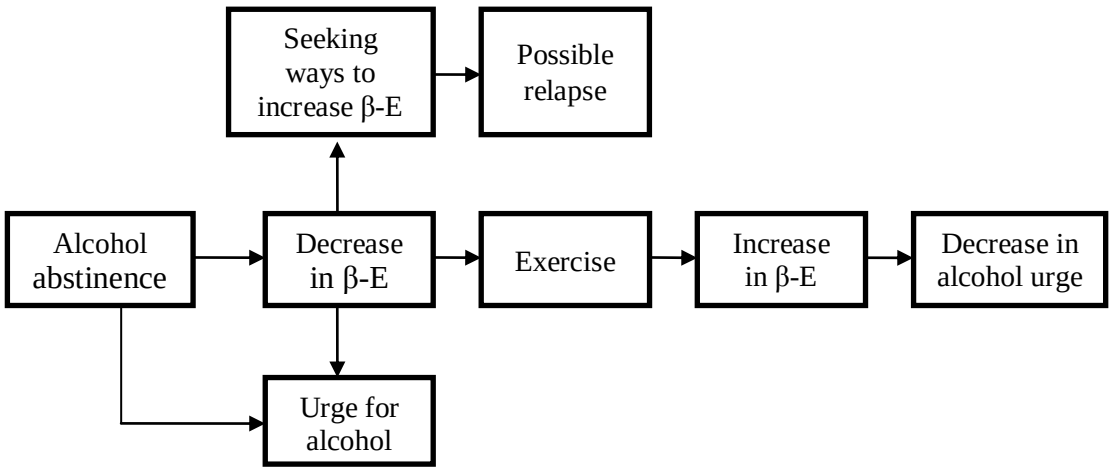


Figure 1: Schematic representation of a proposed model of the possible relationship between alcohol urge, β-E levels and physical exercise (Adapted from Zourbanos et al., 2011)

Additionally, it has been mentioned already that the MDS is thought to play a central role in the development of alcohol dependence. The reinforcing effects of alcohol are partially mediated by the MDS through interactions of certain opioid peptides with opioid receptors that increase dopamine release in the nucleus accumbens (Koob, 1992). Although the brain regions that underlie the reinforcing effects of exercise are not known, there are

some data suggesting that exercise generally activates the same reward pathways that are activated by alcohol or other addictive substances use. It has been found that acute bouts of exercise increase dopamine levels (Heyes et al., 1988; Hattori et al., 1994; Meeusen et al., 1997; Petzinger et al., 2007), and chronic exercise programmes result in sustained increases in dopamine levels (Gilliam et al., 1984; MacRae et al., 1987; Fisher et al., 2004). Given that increases in dopamine levels in the MDS mediate the reinforcing effects of alcohol and exercise may favorably affect the MDS, it is suggested that exercise could be a useful tool for prevention and treatment of AUDs.

Furthermore, alcohol consumption stimulates several neuroendocrine responses in the hypothalamic-pituitary-adrenal axis. Alcohol consumption increases the release of corticotropin releasing hormone (CRH), which stimulates POMC and consequently gives rise to ACTH, β-lipotropin and β-E. ACTH stimulates cells of the adrenal cortex in order to increase the release of cortisol, which in turn inhibits the release of CRH and ACTH through a negative feedback mechanism. Opioidergic and gamma-aminobutyric acid (GABA) neurons also inhibit the release of CRH, while serotonergic and noradrenergic neurons stimulate its release (Gianoulakis, 2001). All these neuroendocrine changes caused by alcohol exposure eventually lead to psychological dependence, while the new disturbed levels of neurotransmitters become the norm.

Taken all together, it becomes clear that alcohol ingestion influences many regions in the brain and, unsurprisingly, there are evidence showing that individuals with AUDs often develop neurological and psychological disorders. It has been postulated that alcohol abuse may lead to decreased brain neuroplasticity. Neuroplasticity is brain’s ability to change its neural organization and function in order to adjust to environmental changes, to respond to damage and to receive new information. These changes are thought to be regulated by a neurotrophic family of signaling proteins (neurotrophins) including the brain-derived

neurotrophic factor (BDNF), which has been demonstrated to have several important roles in the regulation of neuronal cell proliferation and survival (Bramham & Messaoudi, 2005; Lykissas et al., 2007). In contrast to alcohol, exercise has been shown to improve neuroplasticity by enhancing cognitive function and increasing the expression and release of neurotransmitters and BDNF (Meussen et al. 2001; Knaepen et al. 2010; Zoladz & Pilc, 2010; Cassilhas et al. 2012; Gallego et al., 2015). Thus it has been suggested that this effect of exercise on BDNF expression in the hippocampus could also offer protection against alcohol-induced damage and lead to decreased alcohol consumption (Gallego et al., 2015).

Moreover, there are gender differences that influence the effects of alcohol in the body. It has been shown that women are more vulnerable to the effects of alcohol consumption than men due to physiological differences, as they usually have lower body weight percentage, higher body fat percentage and lower body fluid percentage. Thus women have a higher risk of alcohol dependence, liver cirrhosis and tissue damage than men. In addition to that, gender differences may also influence the effects of exercise on AUDs. Recently, a study using male and female C57BL/6 adolescent mice was conducted to evaluate the effect of voluntary exercise (wheel running) on alcohol consumption and preference. The results showed that voluntary exercise resulted in decreased ethanol consumption and preference only in female mice, indicating that there were gender differences in the efficacy of voluntary exercise and its effects on alcohol-related behaviours (Gallego et al., 2015).

3. METHODOLOGY

3.1. STUDY 1 (ACUTE EXERCISE IN ALCOHOLIC PATIENTS)

3.1.1. SUBJECTS

Nine chronic alcoholic patients (eight males and one female) who had undergone alcohol detoxification in a psychiatric clinic in Greece and nine healthy controls volunteered to participate. Patients were diagnosed as being alcohol dependent according to the DSM-IV and the AUDIT (AUDIT score > 20; Moussas et al., 2009). A medical exam showed that alcoholic patients had no cardiovascular or metabolic disease. However, five patients were receiving antidepressant medicine, five were receiving anticonvulsant medicine (two subject were receiving both) and seven patients were receiving vitamin supplements (B1, B6, B12 and folic acid).

3.1.2. EXPERIMENTAL DESIGN

Subjects were informed about the study protocol, the associated risks and benefits and they signed an informed consent form. All subjects participated in a trial of low intensity (55-60% of the Maximum Heart Rate) exercise for 30 minutes on a cycle ergometer (Monark Vansbro, Sweden) in the morning. Alcoholic patients participated in the trial 10-14 days after hospitalization. Heart rate was monitored continuously during exercise by short-range telemetry (Sports Tester PE 3000, Polar Electro, Kempele, Finland). Alcohol urge questionnaire (AUQ) was filled and blood samples were collected prior to and immediately after exercise. The procedures were in accordance with the 1975 Declaration

of Helsinki and ethics approval was received from the University of Thessaly review board.

3.1.3. BLOOD COLLECTION AND HANDLING

Blood samples were drawn from a forearm vein and then were handled as follows:

- A small portion of blood was collected into ethylenediamine tetra acetic acid (EDTA) tubes and shaken thoroughly for the determination of complete blood count (CBC) and lactic acid (LAC).
- For preparation of plasma for β-E determination, another portion of blood was collected in vacutainer tubes containing EDTA and Trasylol® (5000 KIU Trasylol in a 10 ml vacutainer tube) shaken thoroughly and cooled in an ice-bath. Plasma was separated by centrifugation at 1370 x g for 10 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80^{o}C until assayed.
- For serum separation, another portion of blood was also collected in tubes containing clot activator, left at room temperature for 20 min to clot, and centrifuged at 1370 x g for 10 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80^{o}C for later determination of aspartate transaminase (AST), alanine transaminase (ALT) and γ-glutamyl transferase (γ-GT).

3.1.4. METHODS

Anthropometric and physiological measurements

Body weight was measured to the nearest 0.1 kg (Tanita Body Fat Monitor/Scale TBF-521; Tanita, Inc., IL, USA), with subjects lightly dressed and barefoot. Standing height

was measured to the nearest 0.1 cm (Stadiometer 208; Seca, Birmingham, UK). Blood pressure (BP) was measured with a manual sphygmomanometer (FC-101 Aneroid Sphygmomanometer; Focal Corporation, Japan).

Blood samples analyses

All sample assays were performed in duplicate.

Assays in whole blood: CBC [white blood cell (WBC), lymphocytes (LYM), monocytes (MON), granulocytes (GRA), lymphocyte percentage (LYM%), monocyte percentage (MON%), granulocyte percentage (GRA%), red blood cell count (RBCc), hemoglobin (HGB), hematocrit (Hct), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red blood cell distribution width (RDW), platelets (PLT), mean platelet volume (MPV), platelecrit (PCT), platelet distribution width (PDW)] was measured with a Mythic 18 (Orphee S.A., Geneva, Switzerland) autoanalyser. LAC was determined with miniphotometer (Dr. Lange Miniphotometer plus LP 20, Hach Lange, Berlin, Germany) using commercially available cuvette tests (Hach Lange, Berlin, Germany).

Assays in plasma: β-E levels were measured using a human RIA (Radioimunoassay) diagnostic kit (KIPERB301; DIASource Europe SA, Belgium) for human plasma β-E with negligible cross reactivity against other human polypeptides. The inter-assay and intra-assay variation was 7.2% and 7.1%, respectively.

Assays in serum: AST, ALT and γ-GT were measured photometrically in a Clinical Chemistry Analyzer Z 1145 (Zafiropoulos Diagnostica, Athens, Greece) by the IFCC - UV Kinetic Method with commercially available kits (Zafiropoulos, Athens, Greece).

Alcohol Urge Questionnaire

The Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995) consists of 8 questions (1 = strongly disagree, 7 = strongly agree). Subjects were asked to describe their current feelings based on the instructions that were provided to them, not as they wished to feel in the future. They were also informed that there were no right or wrong answers and that their responses would remain anonymous and confidential. Cronbach's alpha coefficient before exercise was 0.68 and immediately after exercise was 0.70.

3.1.5. STATISTICAL ANALYSIS

Two-way repeated measures ANOVA was conducted to analyze the data. If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis using the Bonferroni test method. Pearson correlation was performed to assess a possible correlation between changes in β-E and alcohol urge.

The level of statistical significance was set at $p < .05$. The statistical programme used for all analyses was SPSS version 15.0 (SPSS Inc., USA).

3.2. STUDY 2 (EXERCISE TRAINING INTERVENTION IN HEAVY DRINKERS)

3.2.1. SUBJECTS

Eleven (age: 30.3 ± 3.5 yrs; BMI: 28.4 ± 0.86 kg/m^2) men participated in an 8-week supervised ET intervention. All subjects were sedentary and used to drink heavily. The level of physical activity was assessed by the International Physical Activity

Questionnaire (IPAQ). Subjects were identified as being heavy alcohol drinkers by fulfilling the criteria of at least one of the two following definitions:

(1) Men drinking more than 14 drinks per week or 4 drinks per occasion (1 drink = 14 grams of pure alcohol; definition of the NIAAA for drinking at low risk for developing an AUD; NIAAA, 2014)

(2) Individuals drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days (1 drink = 14 grams of pure alcohol; definition of the Substance Abuse and Mental Health Services Administration for heavy drinking; NIAAA, 2014).

Moreover, the Alcohol Use Disorders Identification Test (Moussas et al., 2009), which is a tool for identifying individuals with hazardous and harmful patterns of alcohol consumption, was used (WHO, 2001). At the baseline, four heavy drinkers had a score of 8-15, three heavy drinkers had a score of 16-19, and four heavy drinkers had a score of 20 or above (total AUDIT score: 17.45 ± 1.60).

Exclusion criteria included serious health problems, physical disabilities or any other medical condition that contraindicate safe participation in exercise, according to medical record; any person with a history of drug abuse other than alcohol; any person aged sixty and over. Moreover, women were also excluded from the study due to physiological differences between genders.

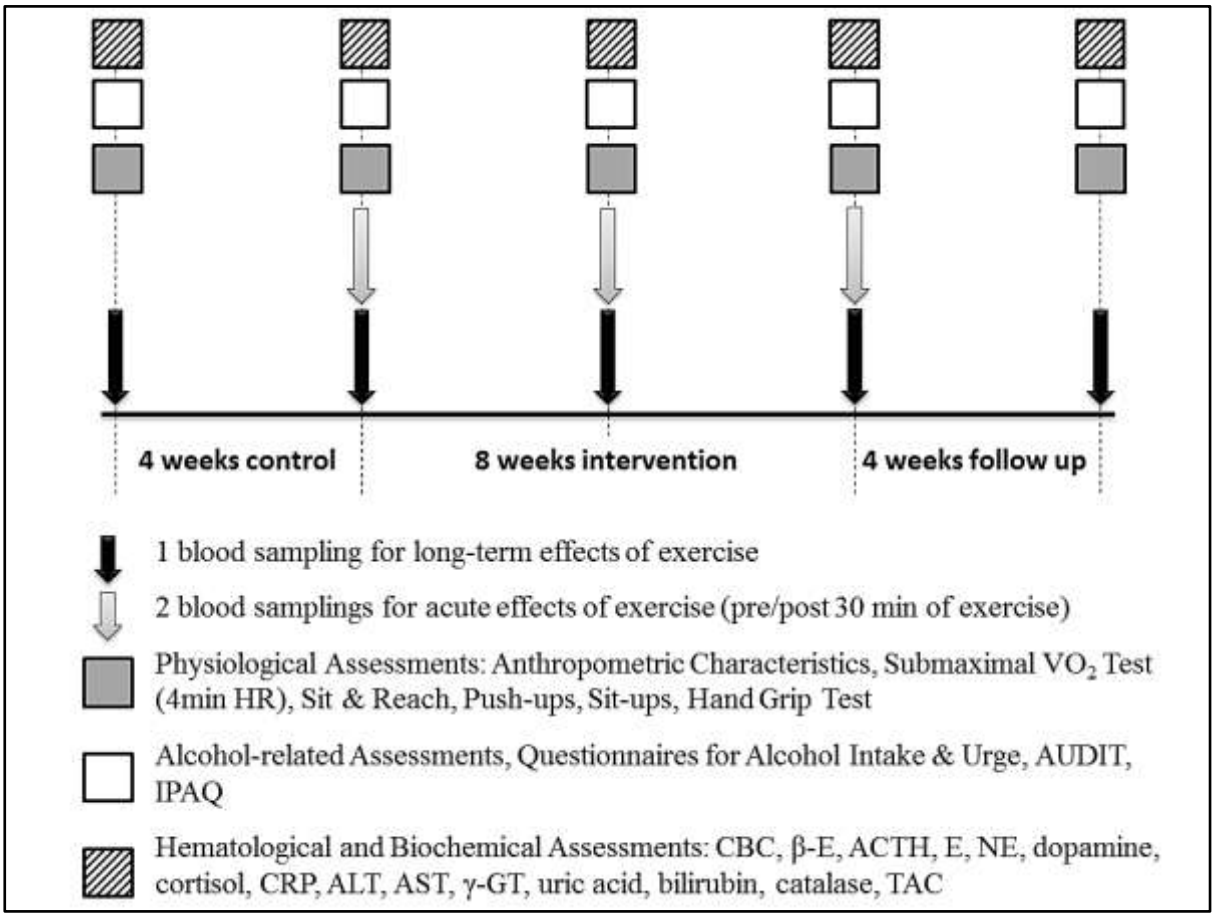
There were two drop-outs; one man left the programme after completing the first 3 weeks of the ET intervention due to personal reasons and one man was excluded from the study after 5 weeks of ET intervention due to low compliance with the programme (he would not come to most of the exercise sessions due to hangover symptom, e.g. headache, weakness).

3.2.2. EXPERIMENTAL DESIGN

Recruitment of the subjects included flyers, posters, media advertisements, and word-of-mouth recruiting all over the region of Thessaly, Greece. Screening questionnaires were used in order to examine whether volunteers fulfilled the criteria. Subjects were informed about the study protocol, the associated risks and benefits and they signed an informed consent form. Before proceeding to other measurements, medical history was reviewed and a resting electrocardiogram (ECG) was performed on each subject in order to detect any heart abnormalities and contraindications to exercise. The procedures were in accordance with the 1975 Declaration of Helsinki and ethics approval was received from the University of Thessaly review board.

Before intervention, subjects were asked to record their daily alcohol intake without changing their physical activity levels for four weeks (control condition). During the 8-week supervised ET intervention, subjects were also recording their daily alcohol intake and were motivated to increase gradually the duration and frequency of ET. Physiological, hematological, biochemical and other measurements were performed in the control condition, in the ET intervention (pre/mid/post), as well as in a 4-week follow up period. A diagram of the design is shown in Figure 2. A more detailed description of all the measurements conducted throughout the study is presented next.

Figure 2: Schematic presentation of the study protocol.



- *Control condition, ET intervention (pre/mid/post) and follow up measurements*:
  - Physiological assessments: Anthropometric Characteristics, Submaximal VO_2 Test (4min HR), Sit & Reach, Push-ups (number of push-ups until exhaustion), Sit-ups (number of sit-ups in 1 min), Hand Grip Test
  - Biochemical assessments: β-E, Catecholamines, Cortisol, Liver Enzymes (ALT, AST, γ-GT), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), LAC, CBC
  - Antioxidant status assessments: uric acid (UA), bilirubin, total antioxidant capacity (TAC), catalase
  - Other assessments: IPAQ, Questionnaires for Alcohol Intake & Urge, AUDIT

3.2.3. BLOOD COLLECTION AND HANDLING

Before intervention, blood samples were collected in the control condition (the post-control condition time point was also the pre-intervention time point). Blood samples were also collected at the end of the 4th (mid-intervention) and 8th (post-intervention) week of intervention, as well as 4 weeks after intervention (follow up).

Before the first blood sample collection, participants were instructed to record their diet for two days and to follow the same diet before each next blood sample collection. Participants were also asked to refrain from any strenuous physical activity for at least two days before each blood sample collection. Blood samples were collected in the morning (8:00 - 10:00 a.m.) after an overnight fast and smoking abstinence.

Blood samples were drawn from a forearm vein and then were handled as follows:

- A small portion of blood was collected into EDTA tubes and shaken thoroughly for the determination of CBC, ESR and LAC.
- For plasma preparation, another portion of blood was placed in separate tubes mixed with EDTA (20 μL/mL of blood), shaken thoroughly and centrifuged at 1370 x g for 10 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80^{o}C for later determination of adrenocorticotropin ACTH, catecholamines (E, NE and dopamine) and TAC.
- For red blood cell lysate preparation, packed erythrocytes were diluted with distilled water (1:1 v/v), vortexed vigorously, and centrifuged at 4000 x g for 15 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and stored at -80 ^{o}C for later determination of catalase activity levels.
- For preparation of plasma for β-E determination, another portion of blood was collected in vacutainer tubes containing EDTA and Trasylol® (aprotinin), shaken

thoroughly and cooled in an ice-bath immediately until centrifugation at 1370 x g for 10 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80^{o}C until assayed.

- For serum separation, another portion of blood was also collected in tubes containing clot activator, left at room temperature for 20 min to clot, and centrifuged at 1370 x g for 10 min at 4^{o}C. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80^{o}C for later determination of cortisol, CRP, AST, ALT, γ-GT, UA and bilirubin.

3.2.4. METHODS

Anthropometric and physiological measurements

Body weight was measured to the nearest 0.1 kg (Tanita Body Fat Monitor/Scale TBF-521; Tanita, Inc., IL, USA), with subjects lightly dressed and barefoot. Standing height was measured to the nearest 0.1 cm (Stadiometer 208; Seca, Birmingham, UK). Percentage body fat was assessed using the bioelectrical impedance analysis technique (Tanita Body Fat Monitor/Scale TBF-521; Tanita, Inc., IL, USA). Blood pressure (BP) was measured with a manual sphygmomanometer (FC-101 Aneroid Sphygmomanometer; Focal Corporation, Japan).

4min HR: Maximal oxygen uptake (VO2max, ml.kg-1.min-1) was estimated based on a Single Stage Submaximal Treadmill Walking Test (SSTWT), which can be used by individuals of various ages and fitness levels (Ebbeling et al., 1991).

Blood samples analyses

Each variable was analyzed in duplicates on the same day. Samples had undergone only one freeze-thaw cycle.

Assays in whole blood: CBC was measured with a Mythic 18 (Orphee S.A., Geneva, Switzerland) autoanalyser. LAC was determined with miniphotometer (Dr. Lange Miniphotometer plus LP 20, Hach Lange, Berlin, Germany) using commercially available cuvette tests (Hach Lange, Berlin, Germany). ESR was measured by the Wintrobe method. All indices were determined on the day of blood collection.

Assays in plasma: Catecholamines and β-E were determined by ^{125}I – radioimmunoassay with commercially available kit (BIO SOURCE Europe S.A., Nivelles, Belgium). ACTH was determined by ^{125}I – radioimmunoassay with commercially available kit (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany). TAC was determined by a method based on the scavenging of 1,1-diphenyl-2-picrylhydrazyl, according to Janaszewska and Bartosz (2002).

Assays in serum: Cortisol was determined by ^{125}I – radioimmunoassay with commercially available kit (IMMUNOTECH S.A., a Beckman Coulter Company, Prague, Czech Republic). CRP was determined by a semi-quantitative latex slide test (Zafiropoulos Diagnostica S.A., Athens, Greece). AST, ALT and γ-GT were measured photometrically in a Clinical Chemistry Analyzer Z 1145 (Zafiropoulos Diagnostica, Athens, Greece) by the IFCC - UV Kinetic Method with commercially available kits (Zafiropoulos, Athens, Greece). UA and bilirubin were measured in a Clinical Chemistry Analyzer Z 1145 (Zafiropoulos Diagnostica, Athens, Greece) with commercially available kits (Zafiropoulos, Athens, Greece).

Assays in red blood cell lysate: Catalase activity was determined according to a method by Aebi (1984).

3.2.5. STATISTICAL ANALYSIS

Two-way repeated measures ANOVA was conducted to examine differences in alcohol intake, alcohol-related outcomes, physiological, hematological and biochemical indices between the control condition and the 8-week ET intervention (2 conditions: control/training; 2 time points: pre/post; n=11). If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis using the Bonferroni test method.

One-way repeated measures ANOVA was conducted to examine the effects of the 8-week ET intervention in alcohol intake, alcohol-related outcomes, physiological, hematological and biochemical indices (3 time points: pre-, mid-, post- ET intervention).

Two-way repeated measures ANOVA was conducted to examine differences in alcohol intake, alcohol-related outcomes, physiological, hematological and biochemical indices between the 8-week ET intervention and the follow up (2 conditions: control/follow up; 2 time points: pre/post; n=8). If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis using the Bonferroni test method. Pearson correlation was performed to assess a possible correlation between changes in β-E and other indices.

Data are presented as mean ± SE. The level of statistical significance was set at $p < .05$. The statistical programme used for all analyses was SPSS version 18.0 (SPSS Inc., USA).

3.3. STUDY 3 (TRIALS OF ACUTE EXERCISE IN HEAVY DRINKERS)

3.3.1. SUBJECTS

Eleven heavy drinkers that participated in the ET intervention also participated in 3 trials of acute exercise (pre-, mid-, post- ET intervention).

3.3.2. EXPERIMENTAL DESIGN

Subjects performed 3 trials of acute exercise. Each trial involved 30 min of exercise of moderate intensity (50-60% HRR) on cycle ergometer (Monark Ergomedic 874E, Monark AB, Vansbro, Sweden). Heart rate was monitored during exercise sessions and trials by short-range telemetry (Polar RC3 GPS HR, Polar Electro, Kempele, Finland). Study protocol is shown in Figure 2.

- *Trials of acute exercise (time points where trials conducted: pre-, mid-, post-intervention)*:
  - Physiological and other assessments before exercise: Anthropometric Characteristics, Submaximal VO_2 Test, Sit & Reach, Push-ups (number of push-ups until exhaustion), Sit-ups (number of sit-ups in 1 min), Hand Grip Test, IPAQ, AUDIT, Questionnaires for Alcohol Intake
  - Biochemical assessments pre- and post- exercise: β-E, Catecholamines, Cortisol, Liver Enzymes, CRP, ESR, lactic acid, CBC
  - Antioxidant status assessments: UA, bilirubin, TAC, catalase

- Other assessments pre-, during (every 5 min), post- exercise: Borg Scale (Rate of Perceived Exertion - RPE), Heart Rate, Revolutions Per Minute (rpm)
- Other assessments pre-, during (every 5 min), post- exercise and every 15 min after exercise for 1 hour: AUQ

Blood samples were collected in the morning (8:00 - 10:00 a.m.) after overnight fast and smoking abstinence. Trials were conducted in a thermoregulated laboratory.

3.3.3. BLOOD COLLECTION AND HANDLING

Blood samples were drawn from a forearm vein and then were handled as described in the subchapter 3.2.3.

3.3.4. METHODS

Each variable was analyzed in duplicates on the same day. Samples had undergone only one freeze-thaw cycle. Analyses were conducted as described in the subchapter 3.2.4.

3.3.5. STATISTICAL ANALYSIS

Two-way repeated measures ANOVA was conducted to examine differences in alcohol intake, alcohol-related outcomes, physiological, hematological and biochemical indices between the acute trials (3 conditions: exercise trial before the beginning of the 8-week ET intervention, exercise trial at the end of the 4^{th} week of ET intervention, exercise trial at the end of the 8^{th} week of ET intervention; 2 time points: pre-, post-exercise; n=11). If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis using the Bonferroni test method. Pearson

correlation was performed to assess a possible correlation between changes in β-E and other indices.

Data are presented as mean ± SE. The level of statistical significance was set at $p < .05$. The statistical programme used for all analyses was SPSS version 18.0 (SPSS Inc., USA).

3.4. STUDY 4 (TRIAL OF ACUTE EXERCISE IN HEAVY DRINKERS Vs CONTROLS)

3.4.1. SUBJECTS

Eleven male heavy drinkers (EG - age: 30.3 ± 3.5 yrs; BMI: 28.4 ± 0.86 kg/m^2) and 11 matched controls (CG - age: 34.1 ± 2.0 yrs; BMI: 27.0 ± 1.67 kg/m^2) participated in a trial of acute exercise. All subjects were sedentary and 8 subjects in each group were smokers.

3.4.2. EXPERIMENTAL DESIGN

The trial involved 30 min of exercise of moderate intensity (50-60% HRR) on a cycle ergometer (Monark Ergomedic 874E, Monark AB, Vansbro, Sweden). Heart rate was monitored during exercise by short-range telemetry (Polar RC3 GPS HR, Polar Electro, Kempele, Finland).

Blood samples were collected prior to and immediately after exercise. The trial was conducted in a thermoregulated laboratory in the morning (8:00 - 10:00 a.m.) after an overnight fast and smoking abstinence,

3.4.3. BLOOD COLLECTION AND HANDLING

Blood samples were drawn from a forearm vein and then were handled as described in the subchapter 3.2.3.

3.4.4. METHODS

Each variable was analyzed in duplicates on the same day. Samples had undergone only one freeze-thaw cycle. Analyses were conducted as described in the subchapter 3.2.4.

3.4.5. STATISTICAL ANALYSIS

Two-way repeated measures ANOVA was conducted to examine differences in physiological, hematological and biochemical indices between the two groups. If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis using the Bonferroni test method. Pearson correlation was performed to assess a possible correlation between changes in β-E and other indices.

Data are presented as mean ± SE. The level of statistical significance was set at $p < .05$. The statistical programme used for all analyses was SPSS version 18.0 (SPSS Inc., USA).

4. RESULTS

4.1. STUDY 1 (ACUTE EXERCISE IN ALCOHOLIC PATIENTS)

Anthropometric and physiologic characteristics of the subjects are presented in Table 5. All alcoholic patients had a history of addiction of at least 10 years. The mean relative exercise heart rate did not differ between alcoholic patients and healthy controls. AUDIT score of alcoholic patients was high, indicating alcohol dependence.

Table 5: Anthropometric, physiological and other characteristics of alcoholic patients and controls.

Variable	Alcoholics	Controls
Age (yrs)	41.2 ± 6.7	38.2 ± 10.7
Weight (kg)	75.0 ± 12.9	73.2 ± 11.9
Height (m)	171.0 ± 6.7	170.3 ± 8.7
% Body Fat	20.3 ± 12.0	21.3 ± 9.8
Flexibility (cm)	17.8 ± 10.1	18.8 ± 8.1
Push-Ups	14.3 ± 6.0	16.1 ± 8.0
Sit-Ups	17.3 ± 3.3	15.3 ± 4.3
Exercise Heart Rate (bpm)	110.5 ± 18.4	114.1 ± 21.4
% Maximal Heart Rate	61.1 ± 4.9	62.2 ± 3.5
AUDIT score	28.6 ± 6.4[1]	0.0 ± 0.0

[1]Significantly different from controls ($p<.05$).

4.1.1. HEMATOLOGICAL PARAMETERS

Concerning CBC parameters, there was a significant effect of time for RBCc, Hb and Hct (Table 6).

Table 6: CBC parameters of alcoholic patients and controls before and immediately after exercise.

Index	Alcoholics Pre-exercise	Alcoholics Post-exercise	Controls Pre-exercise	Controls Post-exercise	Normal rage
WBC (10^3/μl)	8.7 ± 1.9	8.8 ± 1.9	6.8 ± 1.1	7.7 ± 1.4	4.0-12.0
LYM %	27.93 ± 5.45	26.4 ± 4.9	32.2 ± 5.3	35.1 ± 7.3	25.0-50.0
MON %	9.04 ± 2.46	9.6 ± 2.8	11.2 ± 3.6	11.1 ± 4.0	2.0-10.0
GRA %	63.01 ± 5.34	64.0 ± 5.4	56.6 ± 6.7	53.7 ± 8.5	50.0-80.0
RBCc (10^6/μl)	4.32 ± 0.43	4.4 ± 0.4[1]	4.6 ± 0.4	4.8 ± 0.3[1]	4.00-6.20
HGB (g/dl)	14.46 ± 1.11	14.8 ± 1.2[1]	13.6 ± 0.9	14.2 ± 0.9[1]	11.0-18.0
HCT %	42.2 ± 3.42	43.0 ± 3.4[1]	41.5 ± 2.3	43.6 ± 2.3[1]	35.0-55.0
MCV (μm^3)	97.7 ± 2.8	97.6 ± 29.1	90.5 ± 3.0	90.5 ± 3.2	80.0-100.0
MCH (pg)	33.5 ± 1.1	33.3 ± 35.3	29.7 ± 1.4	29.5 ± 1.2	26.0-34.0
MCHC (g/dl)	34.2 ± 0.6	34.1 ± 0.6	32.9 ± 1.3	32.7 ± 1.5	31.0-35.5
RDW %	13.8 ± 1.3	13.8 ± 1.5	11.8 ± 0.6	11.7 ± 0.7	10.0-16.0
PLT (10^3/μl)	240.89 ± 54.89	251.6 ± 54.0	263.9 ± 68.3	247.4 ± 110.0	150-400
MPV (μm^3)	9.1 ± 1.2	9.3 ± 1.6	8.1 ± 0.8	8.2 ± 0.7	7.0-11.0

[1]Significantly different from pre-exercise at the same group.

4.1.2. BIOCHEMICAL PARAMETERS

Pre-exercise levels of lactic acid were not significantly different between groups and they significantly increased ($p<0.001$) after exercise in both groups.

Pre-exercise β-E levels were significantly lower ($p<0.001$) in alcoholic patients compared to controls. Exercise resulted in significant increased ($p<0.001$) β-E levels in alcoholic patients, which were not significant different from the ones in control group (Table 7).

Table 7: Biochemical parameters of alcoholic patients and controls before and immediately after exercise.

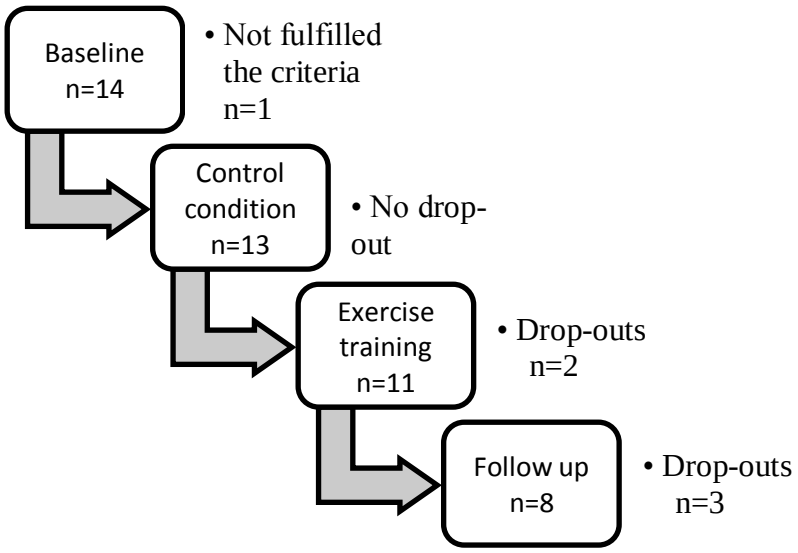
Index	**Alcoholics Pre-exercise**	**Alcoholics Post-exercise**	**Controls Pre-exercise**	**Controls Post-exercise**	**Normal range**
LAC (mmol/L)	1.2 ± 0.1	2.8 ± 0.5	1.3 ± 0.5	3.2 ± 0.5	0.5-2.2 (at rest)
AST (U/L)	46.8 ± 29.2	54.4 ± 37.6	N/A	N/A	Men: ≤37; Women: ≤31
ALT (U/L)	50.8 ± 35.4	53.9 ± 35.0	N/A	N/A	Men: ≤42; Women: ≤32
CRP (mg/L)	1.03 ± 0.81	1.35 ± 0.81	N/A	N/A	<6 mg/L
β-E (pmol/L)	1.6 ± 0.4	4.8 ± 1.6	8.3 ± 4.1	9.0 ± 3.4	

[1]Significantly different from pre-intervention.

4.2. STUDY 2 (EXERCISE TRAINING INTERVENTION IN HEAVY DRINKERS)

Fourteen men were interested in participating in the study. After screening, one man was excluded since his medical record revealed health problems where exercise is contraindicated. Finally, thirteen men fulfilled the criteria and consented to participate in the study. All of the subjects that completed the 4-week control condition and then enrolled to the 8-week supervised ET intervention. During the ET there were two drop-outs (21.4 %) and eleven subjects completed the intervention. All of the subjects that completed the ET intervention were informed that there would be a 4-week follow up period but the drop-out rate increased (27.3%) with eight subjects completing this phase of the study (Figure 3).

Figure 3: Number of subjects that completed each phase of the study.



The two subjects that dropped out during ET intervention are not included in the control condition as well. Anthropometric and physiological characteristics of the subjects that completed the 8-week ET intervention (n=11) are summarized in Table 8. The

measurements were performed at the baseline (just before the beginning of the control condition).

Table 8: Anthropometric and physiological characteristics of the subjects (n=11) at the baseline.

Characteristic	Value
Age	30.3 ± 3.5
Height (cm)	176.9 ± 2.1
Weight (kg)	88.9 ± 3.1
BMI (kg/m^2)	28.4 ± 0.9

Most of the subjects were smokers 72.73% while no other substance abuse was present. As regards to employment at the time of enrollment to the study, 27.27% of the subjects had been employed as professionals or skilled workers, 27.27% had been employed as unskilled workers, and 45.46% were university students. Concerning personal life, 27.27% of the subjects were married, 9.09% were living with a partner, 18.18% were living with their parents and siblings, and 45.46% were living alone being single. The majority of the subjects (72.73%) had secondary education according to the United Nations Educational, Scientific and Cultural Organization (2011; Table 9).

Table 9: Education level of the subjects.

Level of Education[1]	% Percentage
ISCED level 3 – Upper secondary education	72.73
ISCED level 6 – Bachelor's or equivalent level	18.18
ISCED level 8 – Doctoral or equivalent level	9.09

1According to the United Nations Educational, Scientific and Cultural Organization (2011).

Table 10 shows mean values for nutrient content of the two-day diet records of the subjects. Paired t-test did not reveal any significant difference in nutrient content between the two days.

Table 10: Nutrient analysis of the two-day diet records of the subjects.

Value	1st day	2nd day
Energy (kcal)	2221.8 ± 196.8	2005.35 ± 226.1
Total Proteins (g)	83.5 ± 11.4	72.8 ± 9.7
Total Carbohydrates (g)	200.6 ± 29.0	205.4 ± 30.4
Sugar (g)	42.3 ± 16.7	21.9 ± 9.9
Fiber (g)	11.7 ± 2.4	11.0 ± 1.8
Total Fat (g)	96.3 ± 8.4	82.5 ± 12.0
Saturated fats (g)	29.7 ± 2.8	27.9 ± 4.5
Monounsaturated fats (g)	43.8 ± 3.8	34.5 ± 6.1
Polyunsaturated fats (g)	12.0 ± 1.6	10.6 ± 1.6
Cholesterol (mg)	386.4 ± 86.4	239.3 ± 36.3
Alcohol (g)	61.4 ± 11.5	37.6 ± 8.6
Caffeine (mg)	184.0 ± 35.4	176.7 ± 54.3
Manganese - Mn (mg)	2.5 ± 0.4	2.8 ± 0.6
Copper - Cu (mg)	1.3 ± 0.3	1.1 ± 0.2
Zinc - Zn (mg)	9.5 ± 1.2	8.7 ± 1.4
Iron - Fe (mg)	12.5 ± 1.7	11.1 ± 1.6
Selenium - Se (μg)	121.5 ± 14.2	119.3 ± 17.5
Calcium - Ca (mg)	825.7 ± 93.2	781.5 ± 184.8
Potassium - K (mg)	2233.5 ± 255.6	1982.4 ± 352.3
Magnesium - Mg (mg)	261.0 ± 30.0	257.8 ± 39.0
Sodium - Na (mg)	2345.6 ± 284.6	2362.7 ± 494.4
Phosphorus - P (mg)	1257.1 ± 131.5	1148.7 ± 164.4
Vitamin A (IU)	5102.1 ± 1777.4	4548.3 ± 2144.7

Vitamin A (μg RE)	975.0 ± 436.9	645.7 ± 229.6
Vitamin C (mg)	59.2 ± 16.4	59.2 ± 16.2
Vitamin D (IU)	123.3 ± 41.4	121.9 ± 54.1
Vitamin E (mg RE)	6.6 ± 0.9	4.9 ± 0.9
Vitamin B1 (mg)	1.7 ± 0.2	1.7 ± 0.3
Vitamin B2 (mg)	2.0 ± 0.2	2.4 ± 0.8
Vitamin B6 (mg)	1.7 ± 0.3	1.7 ± 0.3
Vitamin B12 (μg)	5.8 ± 2.7	4.4 ± 1.3
Niacin (mg)	25.6 ± 5.1	26.0 ± 4.1
Pantothenic (mg)	4.7 ± 0.6	4.1 ± 0.6
Folic acid (μg)	308.3 ± 35.9	300.2 ± 57.5
Vitamin K (Ug)	68.0 ± 35.5	65.3 ± 27.8

4.2.1. CONTROL Vs EXERCISE TRAINING INTERVENTION

No differences in baseline values of any parameter between conditions were found. Moreover, no differences before and after control condition were observed in any parameter, indicating that this 4-week period of no intervention did not cause any effect in physiological, hematological, biochemical or other parameters tested.

4.2.1.1. PHYSIOLOGICAL PARAMETERS

Statistical analysis showed that there were no differences in VO_2max, diastolic BP, 4min HR, hip circumference, WHR, handgrip and push-ups between the two conditions. Waist circumference ($p<.01$) decreased, while flexibility ($p=.05$) and sit-ups ($p=.005$) increased after the ET intervention. Moreover, there was a non-significant decrease in weight ($p=.053$), BMI ($p=.58$) and systolic BP after the ET intervention.

4.2.1.2. HEMATOLOGICAL PARAMETERS

No differences in post-intervention values of WBC, LYM, MON, GRA, LYM%, MON%, GRA%, HCT, MCH, PLT, MPV, PCT and PDW were found compared to pre-intervention and control condition. The results showed a significant effect of time for RBCc [$F(2, 20) = 25.489$, $p<.001$]. Pairwise comparisons showed significantly decreased post-intervention levels compared to pre-intervention ($p<.05$) and control condition ($p<.005$). Likewise, the results showed a significant effect of time for HGB [$F(2, 20) = 9.096$, $p<.005$]. Pairwise comparisons showed a significant decrease in post-intervention levels compared to pre-intervention ($p<.01$) and a non-significant decrease in post-intervention levels compared to control condition ($p=.078$). A significant effect of time was observed for MCV [$F(2, 20) = 11.954$, $p<.001$]. Pairwise comparisons showed significantly increased post-intervention levels compared to pre-intervention ($p<.01$) and control condition ($p<.05$). As regards to MCHC, a significant effect of time was also found [$F(2, 20) = 12.278$, $p<.001$]. Pairwise comparisons showed significantly decreased post-intervention levels compared to pre-intervention ($p<.005$) and control condition ($p<.05$). Moreover, there was a significant effect of time for RDW [$F(2, 20) = 6.337$, $p=.01$]. Pairwise comparisons showed a significant increase in post-intervention levels compared to pre-intervention ($p<.05$) and a non-significant increase in post-intervention levels compared to control condition ($p=.074$). Finally, the results showed a significant effect of time for ESR [$F(1.041, 9.368) = 5.175$, $p<.05$]. Pairwise comparisons did not show a significant change in ESR. Detailed results are shown in Table 11.

Table 11: CBC and ESR of the subjects that completed the control condition and exercise training intervention.

Index	Pre-control	Pre-intervention	Post-intervention	Normal rage
WBC (**10^3/µl**)	7.509 ± 0.460	7.709 ± 0.619	7.109 ± 0.389	4.0-12.0
LYM (**10^3/µl**)	2.018 ± 0.157	1.773 ± 0.116	2.209 ± 0.206	1.0-5.0
MON (**10^3/µl**)	0.845 ± 0.097	0.900 ± 0.118	0.664 ± 0.106	0.1-1.0
GRA (**10^3/µl**)	4.655 ± 0.328	5.036 ± 0.544	5.100 ± 0.407	2.0-8.0
LYM **%**	26.955 ± 1.844	24.027 ± 1.929	31.173 ± 2.648	25.0-50.0
MON **%**	11.345 ± 0.934	11.745 ± 1.205	9.191 ± 1.425	2.0-10.0
GRA **%**	61.700 ± 1.435	64.227 ± 2.091	59.636 ± 1.766	50.0-80.0
RBCc (**10^6/µl**)	5.178 ± 0.224	5.197 ± 0.218	4.987 ± 0.210[1,3]	4.00-6.20
HGB (**g/dl**)	14.718 ± 0.302	14.964 ± 0.292	13.973 ± 0.333[2,3]	11.0-18.0
HCT **%**	45.145 ± 0.858	45.227 ± 0.735	44.955 ± 0.709	35.0-55.0
MCV (**µm^3**)	88.436 ± 3.126	88.255 ± 3.144	91.382 ± 3.130[1,3]	80.0-100.0
MCH **(pg)**	28.827 ± 1.023	29.191 ± 1.048	28.373 ± 0.987	26.0-34.0
MCHC **(g/dl)**	32.618 ± 0.324	33.100 ± 0.422	31.055 ± 0.431[1,3]	31.0-35.5
RDW **%**	12.791 ± 0.362	12.855 ± 0.383	13.636 ± 0.359[2,3]	10.0-16.0
PLT (**10^3/µl**)	264.091 ± 14.023	267.727 ± 14.418	263.182 ± 14.923	150-400
MPV (**µm^3**)	7.630 ± 0.125	7.660 ± 0.137	7.670 ± 0.143	7.0-11.0
PCT **%**	0.202 ± 0.010	0.199 ± 0.010	0.202 ± 0.012	0.200-0.500
PDW **%**	14.840 ± 0.348	14.180 ± 0.357	14.240 ± 0.400	10.0-18.0
ESR **(mm/h)**	6.950 ± 1.589	7.100 ± 1.197	14.400 ± 3.989	<20

[1]Significant difference from control condition; [2]Non-significant difference from control condition; [3]Significant difference from pre-intervention; [4]Non-significant difference from pre-intervention.

4.2.1.3. BIOCHEMICAL PARAMETERS

There was a significant effect of time for γ-GT [F(2, 20) = 8.803, p<.005]. Pairwise comparisons showed a significant decrease in post-intervention levels compared to pre-intervention (p<.01) and a non-significant decrease in post-intervention levels compared to control condition (p=.078). Detailed results are shown in Table 12.

Table 12: Biochemical parameters of the subjects that completed the control condition and exercise training intervention.

Index	Pre-control	Pre-intervention	Post-intervention	Normal range
LAC **(mmol/L)**	1.192 ± 0.057	1.253 ± 0.079	1.304 ± 0.082	0.5-2.2 (at rest)
γ-GT **(U/L)**	57.736 ± 10.490	59.745 ± 10.346	49.000 ± 9.588[1,2]	Men: 11-61; Women: 9-39
AST **(U/L)**	29.450 ± 4.237	30.820 ± 4.304	30.520 ± 2.130	Men: ≤37; Women: ≤31
ALT **(U/L)**	25.582 ± 3.715	29.273 ± 3.975	26.864 ± 4.232	Men: ≤42; Women: ≤32
ACTH **(pg/ml)**	35.700 ± 4.763	31.700 ± 4.351	33.900 ± 4.668	10-60 (8-10 a.m.) 6-30 (8-10 p.m.)
E **(pg/ml)**	43.500 ± 3.619	44.000 ± 3.941	41.300 ± 3.850	< 100
NE **(pg/ml)**	258.200 ± 35.906	280.600 ± 38.202	237.500 ± 31.574	< 600
Dopamine **(pg/ml)**	39.300 ± 3.419	39.700 ± 2.910	48.900 ± 6.770	< 100
Cortisol **(nM)**	177.182 ± 26.948	161.545 ± 27.151	175.636 ± 18.045	260-720 (morning) 50-350 (evening)
β-E **(pg/ml)**	2.920 ± 0.209	3.313 ± 0.395	3.483 ± 0.637	

[1]Significant difference from pre-intervention; [2]Non-significant difference from control condition.

4.2.1.4. MARKERS OF ANTIOXIDANT STATUS

Statistical analysis showed that there were no differences in the levels of bilirubin, UA or TAC between the two conditions. There was a significant effect of time for catalase [$F(2, 20) = 4.651$, $p<.05$]. Pairwise comparisons showed that there were non-significant increase in post-intervention levels compared to pre-control ($p=.069$). Detailed results are shown in Table 13.

Table 13: Markers of antioxidant status of the subjects that completed the control condition and exercise training intervention.

Parameter	Pre-Control	Pre-Intervention	Post-Intervention
Bilirubin	0.662 ± 0.070	0.649 ± 0.073	0.579 ± 0.050
UA	6.555 ± 0.477	6.427 ± 0.454	6.223 ± 0.321
Catalase	300.429 ± 18.140	322.531 ± 14.793	340.735 ± 13.311[1]
TAC	1.126 ± 0.051	1.186 ± 0.043	1.101 ± 0.037

[1]Non-significant difference from control condition.

4.2.2. EXERCISE TRAINING INTERVENTION

4.2.2.1. EXERCISE-RELATED PARAMETERS

There was a significant effect of time for frequency of ET per week [$F(2, 20) = 9.121$, $p=.005$]. Pairwise comparisons showed a significant increase in post-intervention levels compared to pre-intervention ($p<.05$), and a non-significant increase in post-intervention levels compared to mid-intervention ($p=.086$).

Moreover, there was a significant effect of time for duration of sessions of ET per week [$F(2, 20) = 37.063$, $p<.001$]. Pairwise comparisons showed significantly increased mid-

intervention levels compared to pre-intervention (p<.001), and significantly increased post-intervention levels compared to pre-intervention (p<.001).

Mean HR during sessions of ET per week did not significantly change throughout intervention. Detailed results are shown in Table 14.

Table 14: Exercise-related parameters of the subjects throughout exercise training intervention.

Parameter	Pre-Intervention	Mid-Intervention	Post-Intervention
Frequency of ET (sessions per week)	1.273 ± 0.541	2.614 ± 0.306	3.364 ± 0.237[1,2]
Duration of ET (min per week)	19.091 ± 7.799	96.955 ± 11.476[1]	136.636 ± 16.343[1]
Mean HR during ET per week	133.818 ± 2.470	134.045 ± 3.693	137.432 ± 4.501

[1]Significant difference from pre-intervention; [2]Non-significant difference from mid-intervention. ET: Exercise Training; HR: Heart Rate.

4.2.2.2. PHYSIOLOGICAL PARAMETERS

The 8-week ET intervention had no effect on VO_2max, diastolic BP, 4min HR, WHR, handgrip and push-ups. The results showed that there was a significant effect of time for weight [F(2, 20) = 5.626, p<.05]. Pairwise comparisons showed that there was a non-significant decrease in post-intervention levels compared to mid-intervention (p=.056), and a significant decrease in post-intervention levels compared to pre-intervention (p<.05). There was also a significant effect of time for BMI [F(2, 20) = 5.508, p<.05]. Pairwise comparisons showed that there was a non-significant decrease in post-intervention levels

compared to mid-intervention (p=.057), and a non-significant decrease in post-intervention levels compared to pre-intervention (p=.058). A significant effect of time for systolic BP was observed [F(2, 18) = 4.318, p<.05]. Pairwise comparisons showed that there was a non-significant decrease in mid-intervention levels compared to pre-intervention (p=.070). Moreover, there was a significant effect of time for waist circumference [F(2, 20) = 11.275, p=.001]. Pairwise comparisons showed that there were significantly decreased (p<.05) mid-intervention levels compared to pre-intervention, and significantly decreased (p<.01) post-intervention levels compared to pre-intervention. There was a significant effect of time for flexibility [F(2, 16) = 14.483, p<.001]. Pairwise comparisons showed that there were significantly increased (p<.05) mid-intervention levels compared to pre-intervention, significantly increased (p<.05) post-intervention levels compared to mid-intervention, and significantly increased (p=.01) post-intervention levels compared to pre-intervention. Finally, there was a significant effect of time for sit-ups [F(1.298, 11.679) = 8.852, p<.005]. Pairwise comparisons showed that there were significantly increased (p<.05) mid-intervention levels compared to pre-intervention, and significantly increased (p<.05) post-intervention levels compared to pre-intervention. Detailed results are shown in Table 15.

Table 15: Physiological parameters of the subjects throughout exercise training intervention.

Parameter	Pre-Intervention	Mid-Intervention	Post-Intervention

VO_2max	45.760 ± 1.732	46.270 ± 1.505	49.170 ± 2.464
Weight (kg)	88.845 ± 3.051	89.136 ± 2.906	87.618 ± 3.042[1,4]
BMI (kg/m^2)	28.421 ± 0.863	28.521 ± 0.838	28.027 ± 0.861[2,4]
SBP	121.100 ± 2.470	115.000 ± 2.687[2]	114.100 ± 1.779
DBP	80.700 ± 2.450	77.000 ± 2.134	74.100 ± 1.779
4min HR	121.636 ± 4.575	116.727 ± 3.322	114.273 ± 2.476
Waist	97.445 ± 3.611	94.700 ± 3.133[1]	92.700 ± 3.461[1]
Hip	104.575 ± 1.333	103.887 ± 0.683	102.275 ± 0.724
WHR	0.880 ± 0.025	0.864 ± 0.028	0.859 ± 0.035
Flexibility	10.222 ± 2.520	13.111 ± 2.563[1]	16.389 ± 2.544[1,3]
Handgrip	46.025 ± 1.669	45.000 ± 3.349	47.700 ± 1.791
Sit-ups	27.700 ± 3.183	35.000 ± 2.300[1]	37.300 ± 3.409[1]
Push-ups	15.889 ± 2.383	17.667 ± 2.386	19.222 ± 3.332

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention; [3]Significant difference from mid-intervention; [4]Non-significant difference from mid-intervention.

4.2.2.3. HEMATOLOGICAL PARAMETERS

The 8-week ET intervention did not significantly change the levels of WBC, LYM, MON, GRA, MON%, GRA%, HCT, PLT, MPV, PCT and PDW. There was a significant effect of time for LYM% [F(2, 20) = 4.270, p<.05]. However, pairwise comparisons did not show any significantly change in LYM% throughout intervention. A significant effect of time for RBCc was observed [F(2, 20) = 10.176, p=.001]. Pairwise comparisons showed that there was a significant decrease (p<.001) in post-intervention levels compared to pre-intervention, and also a non-significant decrease (p=.091) in mid-intervention levels compared to pre-intervention. There was a significant effect of time for HGB [F(2, 20) = 12.492, p<.001]. Pairwise comparisons showed that there were significantly decreased

(p<.01) post-intervention levels compared to pre-intervention and also significantly decreased (p<.005) post-intervention levels compared to mid-intervention. There was a significant effect of time for MCV [F(2, 20) = 8.388, p<.005]. Pairwise comparisons showed that there were significantly increased (p<.01) post-intervention levels compared to pre-intervention. Moreover, there was a significant effect of time for MCH [F(2, 20) = 3.948, p<.05]. Pairwise comparisons showed that there were significantly decreased (p<.05) post-intervention levels compared to mid-intervention. There was a significant effect of time for MCHC [F(2, 20) = 12.055, p<.001]. Pairwise comparisons showed that there were significantly decreased (p<.005) post-intervention levels compared to pre-intervention, and also significantly decreased (p<.01) post-intervention levels compared to mid-intervention. There was a significant effect of time for RDW [F(2, 20) = 4.482, p<.05]. Pairwise comparisons showed that there were significantly increased (p<.05) post-intervention levels compared to pre-intervention. Finally, there was a significant effect of time for ESR [F(2, 18) = 5.206, p<.05]. Pairwise comparisons showed that there was a non-significant increase (p=.054) in post-intervention levels compared to mid-intervention. Detailed results are shown in Table 16.

Table 16: CBC and ESR of the subjects throughout exercise training intervention.

Index	Pre-intervention	Mid-intervention	Post-intervention	Normal rage
WBC (**10^3/μl)**	7.709 ± 0.619	7.491 ± 0.427	7.109 ± 0.389	4.0-12.0
LYM (**10^3/μl)**	1.773 ± 0.166	2.064 ± 0.227	2.209 ± 0.206	1.0-5.0

MON (**10^3/μl**)	0.900 ± 0.118	0.782 ± 0.101	0.664 ± 0.106	0.1-1.0
GRA (**10^3/μl**)	5.036 ± 0.544	4.664 ± 0.256	4.236 ± 0.287	2.0-8.0
LYM **%**	24.027 ± 1.929	27.018 ± 2.029	31.173 ± 2.648	25.0-50.0
MON **%**	11.745 ± 1.205	10.527 ± 1.145	9.191 ± 1.425	2.0-10.0
GRA **%**	64.227 ± 2.091	62.455 ± 1.558	59.636 ± 1.766	50.0-80.0
RBCc (**10^6/μl**)	5.197 ± 0.218	5.058 ± 0.203[2]	4.987 ± 0.210[1]	4.00-6.20
HGB (**g/dl**)	14.964 ± 0.292	14.700 ± 0.347	13.973 ± 0.333[1,3]	11.0-18.0
HCT **%**	45.227 ± 0.735	45.064 ± 0.772	44.955 ± 0.709	35.0-55.0
MCV (**μm^3**)	88.255 ± 3.144	90.273 ± 3.112	91.382 ± 3.130[1]	80.0-100.0
MCH **(pg)**	29.191 ± 1.048	29.445 ± 1.152	28.373 ± 0.987[3]	26.0-34.0
MCHC **(g/dl)**	33.100 ± 0.422	32.636 ± 0.618	31.055 ± 0.431[1,3]	31.0-35.5
RDW **%**	12.855 ± 0.383	13.273 ± 0.440	13.636 ± 0.359[1]	10.0-16.0
PLT (**10^3/μl**)	267.727 ± 14.418	261.727 ± 13.327	263.182 ± 14.923	150-400
MPV (**μm^3**)	7.660 ± 0.137	7.560 ± 0.126	7.670 ± 0.143	7.0-11.0
PCT **%**	0.199 ± 0.010	0.198 ± 0.009	0.202 ± 0.012	0.200-0.500
PDW **%**	14.180 ± 0.357	14.670 ± 0.420	14.240 ± 0.400	10.0-18.0
ESR **(mm/h)**	7.100 ± 1.197	8.350 ± 2.311	14.400 ± 3.989[4]	<20

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention; [3]Significant difference from mid-intervention; [4]Non-significant difference from mid-intervention.

4.2.2.4. BIOCHEMICAL PARAMETERS

There was a significant effect of time for γ-GT [$F(2, 20) = 5.880$, $p<.05$]. Pairwise comparisons showed that there were significantly decreased ($p<.01$) post-intervention levels compared to pre-intervention. Detailed results are shown in Table 17.

Table 17: Biochemical parameters of the subjects throughout exercise training intervention.

Index	Pre-intervention	Mid-intervention	Post-intervention	Normal range
LAC **(mmol/L)**	1.253 ± 0.079	1.288 ± 0.094	1.304 ± 0.082	0.5-2.2 (at rest)
γ-GT **(U/L)**	59.745 ± 10.346	54.700 ± 10.951	49.000 ± 9.588[1]	Men: 11-61; Women: 9-39
AST **(U/L)**	29.245 ± 4.199	28.491 ± 2.596	30.191 ± 1.955	Men: ≤37; Women: ≤31
ALT **(U/L)**	29.273 ± 3.975	29.418 ± 3.581	26.864 ± 4.232	Men: ≤42; Women: ≤32
ACTH **(pg/ml)**	30.909 ± 4.015	36.091 ± 4.926	34.455 ± 4.258	10-60 (8-10 a.m.) 6-30 (8-10 p.m.)
E **(pg/ml)**	43.636 ± 3.583	42.455 ± 4.543	40.818 ± 3.516	< 100
NE **(pg/ml)**	275.000 ± 35.006	254.364 ± 29.405	242.000 ± 28.912	< 600
Dopamine **(pg/ml)**	39.455 ± 2.644	41.182 ± 3.357	47.818 ± 6.218	< 100
Cortisol **(nM)**	151.100 ± 27.706	158.000 ± 18.114	167.300 ± 17.692	260-720 (morning) 50-350 (evening)
β-E **(pg/ml)**	3.313 ± 0.395	4.280 ± 0.713	3.483 ± 0.637	

[1]Significant difference from pre-intervention.

4.2.2.5. MARKERS OF ANTIOXIDANT STATUS

The 8-week ET intervention had no effect on bilirubin and UA. The results showed that there was a significant effect of time for catalase [$F(2, 20) = 5.588$, $p<.05$]. Pairwise

comparisons showed that there were significantly increased post-intervention levels compared to mid-intervention ($p<.05$).

Table 18: Markers of antioxidant status of the subjects throughout exercise training intervention.

Parameter	Pre-Intervention	Mid-Intervention	Post-Intervention
Bilirubin	0.649 ± 0.073	0.639 ± 0.066	0.579 ± 0.050
UA	6.427 ± 0.454	6.236 ± 0.338	6.223 ± 0.321
Catalase	322.531 ± 14.793	299.469 ± 18.690	340.735 ± 13.311[1]
TAC	1.186 ± 0.043	1.109 ± 0.035	1.101 ± 0.037

[1]Significant difference from mid-intervention.

4.2.2.6. ALCOHOL-RELATED AND OTHER OUTCOMES

The results showed that there was a significant effect of time for the question "How many alcohol units do you drink per day?" [$F(2, 20) = 3.702$, $p<.05$]. Pairwise comparisons showed that there was a significant decrease in post-intervention levels compared to pre-intervention ($p<.05$).

There was a significant effect of time for the question "How many times did you consume alcohol over the last month?" [$F(2, 20) = 10.276$, $p=.001$]. Pairwise comparisons showed that there was a significant decrease in post-intervention levels compared to pre-intervention ($p=.005$), and a significant decrease in mid-intervention levels compared to pre-intervention ($p<.05$).

There was a significant effect of time for the question "How many AU did you use to drink per occasion over the last month?" [$F(2, 20) = 9.997$, $p=.001$]. Pairwise comparisons

showed that there was a significant decrease in post-intervention levels compared to pre-intervention ($p<.005$), and a significant decrease in mid-intervention levels compared to pre-intervention ($p<.05$).

There was a significant effect of time for the question "How many days do you usually drink alcohol?" [$F(2, 20) = 8.574$, $p<.005$]. Pairwise comparisons showed that there was a significant decrease in post-intervention levels compared to pre-intervention ($p=.01$), and a non-significant decrease in mid-intervention levels compared to pre-intervention ($p=.87$).

There was a significant effect of time for the question "How many AU do you usually drink per week?" [$F(2, 20) = 6.086$, $p<.01$]. Pairwise comparisons showed that there was a significant decrease in post-intervention levels compared to pre-intervention ($p<.005$).

There was a non-significant effect of time for time (min) until first drink after an exercise session [$F(2, 18) = 3.420$, $p=.055$]. Pairwise comparisons showed that there was a significant increase in post-intervention levels compared to pre-intervention ($p<.05$). Detailed results are shown in Table 19.

Table 19: Alcohol use questionnaire scores of the subjects throughout exercise training intervention.

Question	Pre-Intervention	Mid-Intervention	Post-Intervention
How many AU do you drink per day?	3.045 ± 0.605	2.955 ± 0.627	1.955 ± 0.429[1]
How many AU did you drink	2.545 ± 0.455	1.545 ± 0.474	2.455 ± 0.705

last night?			
How many times did you consume alcohol over the last month?	6.818 ± 0.325	5.818 ± 0.464[1]	5.273 ± 0.428[1]
How many AU did you use to drink per occasion over the last month?	5.582 ± 0.512	4.273 ± 0.428[1]	3.682 ± 0.487[1]
How many days do you usually drink alcohol?	5.136 ± 0.463	4.545 ± 0.533[2]	3.864 ± 0.678[1]
How many AU do you usually drink per week?	19.000 ± 3.202	15.864 ± 3.042	11.636 ± 3.032[1]
Would you like to stop drinking alcohol? **(1-10)**	3.909 ± 0.977	4.455 ± 1.003	5.182 ± 0.913
Would you like to cut down on alcohol? **(1-10)**	5.727 ± 0.905	5.636 ± 0.866	6.727 ± 0.810
Time until first drink after an exercise session **(min)**	592.000 ± 88.403	1170.000 ± 387.634	1368 ± 311.615[1]

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention. *AU: Alcohol Units (1 AU = 14 grams of pure alcohol). 1: Not much; 10: Very much.*

Concerning the alcohol units consumed weekly (as recorded by the subjects), there was a significant decrease in post-intervention levels compared to pre-intervention ($p<.05$). Concerning the desire for alcohol over the last week, there was a non-significant decrease in post-intervention levels compared to pre-intervention ($p=.092$), and a non-significant decrease in post-intervention levels compared to mid-intervention ($p=.06$). Detailed results are shown in Table 20.

Table 20: Alcohol-related parameters of the subjects throughout exercise training intervention.

Parameter	Pre-intervention	Mid-Intervention	Post-Intervention
AU consumed over the last week	18.636 ± 3.693	16.727 ± 4.611	12.545 ± 2.654[1]
Desire for alcohol over the last week (0-10)	7.273 ± 0.449	7.273 ± 0.469	6.455 ± 0.545[2,3]
Goal for decrease in alcohol use	3.182 ± 0.464	2.545 ± 0.282	2.727 ± 0.333
How sure are you that you can achieve your goal?	6.727 ± 0.634	7.000 ± 0.739	7.636 ± 0.691

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention; [3]Non-significant difference from mid-intervention. *AU: Alcohol Units (1 AU = 14 grams of pure alcohol).*

Paired t-test showed that there was a significant increase (p=.001) in post-intervention IPAQ values compared to pre-intervention. Moreover, there was a significant decrease (p<.005) in post-intervention AUDIT values compared to pre-intervention. Detailed results are shown in Table 21.

Table 21: Other parameters of the subjects before and after exercise training intervention.

Parameter	Pre-Intervention	Post-Intervention
IPAQ	546.182 ± 119.328	1663.546 ± 270.745[1]
AUDIT score	17.455 ± 1.603	12.818 ± 2.079[1]
% AUDIT score ≤15	36.4	45.5
% AUDIT score >15	63.6	54.5

[1]Significant difference from pre-intervention.

4.2.3. TRAINING INTERVENTION Vs FOLLOW UP

4.2.3.1. PHYSIOLOGICAL PARAMETERS

No significant change in weight, BMI, SBP, DBP, waist, hip, WHR, handgrip between the two conditions was observed. There was a significant effect of time for VO_2max [F(1.155, 6.931) = 10.790, p<.05]. Pairwise comparisons showed that there were significantly increased (p<.05) post-follow up levels compared to pre-intervention. There was also a significant effect of time for 4min HR [F(1.170, 8.188) = 12.687, p<.01]. Pairwise comparisons showed that there were significantly decreased (p<.05) pre- follow up levels compared to pre-intervention and there were also significantly decreased (p<.05) post-follow up levels compared to pre-intervention. A significant effect of time for flexibility was found [F(2, 14) = 4.867, p<.05]. Pairwise comparisons showed that there was a significant increase (p<.05) in pre-follow up levels compared to pre-intervention. Moreover, there was a significant effect of time for sit-ups [F(2, 14) = 12.612, p=.001]. Pairwise comparisons showed that there were significantly increased (p<.05) pre-follow up levels compared to pre-intervention and there were also significantly increased (p<.05) post-follow up levels compared to pre-intervention. Finally, there was a significant effect of time for push-ups [F(1.098, 6.587) = 9.259, p<.005]. Pairwise comparisons showed that there were significantly increased (p<.005) post-follow up levels compared to pre-follow up and there was a significant increase (p<.05) in post-follow up levels compared to pre-intervention. Detailed results are shown in Table 22.

Table 22: Physiological parameters of the subjects that completed the exercise training intervention and follow up.

Parameter	Pre-Intervention	Pre-follow up	Post-follow up
VO_2max	44.857 ± 2.338	46.686 ± 1.941	47.557 ± 1.961[1]
Weight (kg)	90.550 ± 3.990	89.388 ± 3.999	89.300 ± 3.909
BMI (kg/m^2)	29.029 ± 1.025	28.655 ± 1.036	28.617 ± 0.983
SBP	126.750 ± 4.821	118.625 ± 4.412	116.625 ± 3.099
DBP	83.750 ± 3.098	77.375 ± 3.354	78.125 ± 2.302
4min HR	129.500 ± 2.726	117.375 ± 2.291[1]	114.863 ± 3.404[1]
Waist	99.438 ± 4.771	94.813 ± 4.495	96.137 ± 3.736
Hip	106.180 ± 1.707	102.200 ± 1.153	102.540 ± 1.307
WHR	0.866 ± 0.036	0.862 ± 0.055	0.888 ± 0.049
Flexibility	10.313 ± 2.855	14.925 ± 2.653[1]	12.363 ± 2.429
Handgrip	48.792 ± 1.946	50.850 ± 2.073	52.333 ± 1.647
Sit-ups	25.125 ± 2.649	37.138 ± 3.210[1]	37.375 ± 4.031[1]
Push-ups	18.429 ± 2.852	22.443 ± 3.734	28.429 ± 4.613[1,3]

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention; [3]Significant difference from pre-follow up.

4.2.3.2. HEMATOLOGICAL PARAMETERS

There was no change in the levels of WBC, GRA, GRA%, HGB, HCT, MCH, PLT, MPV, PCT, PDW and ESR between the two conditions. There was a significant effect of time for LYM [$F(2, 14) = 3.720$, $p<.05$]. Pairwise comparisons showed that there were significantly increased ($p<.05$) post-follow up levels compared to pre-intervention. There was also a significant effect of time for MON [$F(2, 14) = 4.773$, $p<.05$]. Pairwise comparisons showed that there were significantly decreased ($p<.05$) post-follow up levels compared to

pre-intervention. A significant effect of time for LYM% was found [F(2, 14) = 4.772, p<.05]. Pairwise comparisons showed that there were significantly increased (p<.05) post-follow up levels compared to pre-intervention. There was a significant effect of time for MON% [F(2, 14) = 4.282, p<.05]. Pairwise comparisons showed that there were significantly decreased (p<.05) post-follow up levels compared to pre-intervention. Moreover, a significant effect of time for RBCc was observed [F(2, 14) = 4.666, p<.005]. Pairwise comparisons showed that there were significantly decreased (p<.05) pre-follow up levels compared to pre-intervention. There was a significant effect of time for MCV [F(2, 14) = 10.615, p<.005]. Pairwise comparisons showed that there were significantly increased (p<.01) pre-follow up levels compared to pre-intervention and there were also significantly increased (p<.05) post-follow up levels compared to pre-intervention. There was a significant effect of time for MCHC [F(2, 14) = 9.176, p<.005]. Pairwise comparisons showed that there were significantly decreased (p<.05) pre-follow up levels compared to pre-intervention and there were also significantly decreased (p<.05) post-follow up levels compared to pre-intervention. Finally, there was a significant effect of time for RDW [F(2, 14) = 12.956, p=.001]. Pairwise comparisons showed that there were significantly increased (p<.05) pre-follow up levels compared to pre-intervention and there were also significantly increased (p<.05) post-follow up levels compared to pre-intervention. Detailed results are shown in Table 23.

Table 23: CBC and ESR of the subjects that completed the exercise training intervention and follow up.

Index	Pre-intervention	Pre-follow up	Post-follow up	Normal rage
WBC (**10^3/μl)**	7.413 ± 0.612	6.800 ± 0.418	6.900 ± 0.348	4.0-12.0
LYM (**10^3/μl)**	1.663 ± 0.136	1.912 ± 0.184	2.150 ± 0.146[1]	1.0-5.0

MON (**10^3/µl**)	0.862 ± 0.115	0.712 ± 0.141	0.475 ± 0.062[1]	0.1-1.0
GRA (**10^3/µl**)	4.888 ± 0.591	4.163 ± 0.349	4.225 ± 0.268	2.0-8.0
LYM **%**	23.100 ± 2.063	28.600 ± 3.147	32.425 ± 1.630[1]	25.0-50.0
MON **%**	12.063 ± 1.588	10.300 ± 1.823	6.788 ± 0.662[1]	2.0-10.0
GRA **%**	64.837 ± 2.672	61.100 ± 2.162	60.125 ± 1.285	50.0-80.0
RBCc (**10^6/µl**)	5.320 ± 0.288	5.130 ± 0.270[1]	5.174 ± 0.230	4.00-6.20
HGB (**g/dl**)	15.138 ± 0.373	14.325 ± 0.383	14.275 ± 0.465	11.0-18.0
HCT **%**	45.000 ± 0.955	45.275 ± 0.920	45.725 ± 1.257	35.0-55.0
MCV (**µm^3**)	86.013 ± 3.978	89.700 ± 4.127[1]	89.225 ± 4.299[1]	80.0-100.0
MCH **(pg)**	28.963 ± 1.457	28.375 ± 1.347	27.987 ± 1.421	26.0-34.0
MCHC **(g/dl)**	33.638 ± 0.374	31.612 ± 0.442[1]	31.350 ± 0.334[1]	31.0-35.5
RDW **%**	12.800 ± 0.532	13.813 ± 0.444[1]	14.025 ± 0.386[1]	10.0-16.0
PLT (**10^3/µl**)	268.750 ± 19.262	259.375 ± 17.658	257.375 ± 15.194	150-400
MPV (**µm^3**)	7.888 ± 0.229	7.700 ± 0.168	7.800 ± 0.167	7.0-11.0
PCT **%**	0.212 ± 0.017	0.200 ± 0.012	0.198 ± 0.009	0.200-0.500
PDW **%**	15.350 ± 0.776	14.338 ± 0.410	14.675 ± 0.304	10.0-18.0
ESR **(mm/h)**	7.000 ± 1.464	7.857 ± 2.132	8.429 ± 1.494	<20

[1]Significant difference from pre-intervention.

4.2.3.3. BIOCHEMICAL PARAMETERS

There was no significance change in LAC, AST and ALT levels. There were significant lower ($p<.5$) pre-follow up γ-GT levels than pre-intervention. Detailed results are shown in Table 24.

Table 24: Biochemical parameters of the subjects that completed the exercise training intervention and follow up.

Index	Pre-intervention	Pre-follow up	Post-follow up	Normal range
LAC **(mmol/L)**	1.267 ± 0.101	1.276 ± 0.055	1.173 ± 0.030	0.5-2.2 (at rest)
γ-GT **(U/L)**	63.350 ± 13.338	56.662 ± 12.058[1]	61.650 ± 14.100	Men: 11-61; Women: 9-39
AST **(U/L)**	30.229 ± 5.600	32.400 ± 2.401	32.971 ± 2.506	Men: ≤37; Women: ≤31
ALT **(U/L)**	27.138 ± 3.679	28.387 ± 5.630	27.025 ± 2.908	Men: ≤42; Women: ≤32
ACTH **(pg/ml)**	29.875 ± 3.456	32.375 ± 3.327	32.875 ± 3.734	10-60 (8-10 a.m.) 6-30 (8-10 p.m.)
E **(pg/ml)**	44.250 ± 4.447	44.125 ± 4.151	42.250 ± 4.366	< 100
NE **(pg/ml)**	291.250 ± 47.431	232.750 ± 33.500	210.625 ± 24.718	< 600
Dopamine **(pg/ml)**	40.625 ± 3.453	42.125 ± 3.791	38.500 ± 3.630	< 100
Cortisol **(nM)**	184.625 ± 30.797	185.375 ± 23.790	184.875 ± 29.840	260-720 (morning) 50-350 (evening)
β-E **(pg/ml)**	3.429 ± 0.490	2.929 ± 0.457	2.683 ± 0.292	

[1]Significant difference from pre-intervention.

4.2.3.4. MARKERS OF ANTIOXIDANT STATUS

No significant change in levels of bilirubin, UA and catalase between the two conditions was observed. There was a significant effect of time for TAC [F(1.139, 7.976) = 21.785, p=.001]. Pairwise comparisons showed that there were significantly decreased (p<.05) pre-follow up levels compared to pre-intervention and also significantly decreased (p=.001) post-follow up levels compared to pre-intervention. Detailed results are shown in Table 25.

Table 25: Markers of antioxidant status of the subjects that completed the exercise training intervention and follow up.

Parameter	Pre-Intervention	Pre-follow up	Post-follow up
Bilirubin	0.651 ± 0.096	0.630 ± 0.058	0.660 ± 0.054
UA	6.619 ± 0.547	6.388 ± 0.188	6.496 ± 0.324
Catalase	341.226 ± 15.649	353.369 ± 14.624	364.661 ± 16.334
TAC	1.192 ± 0.059	1.056 ± 0.038[1]	1.045 ± 0.047[1]

[1]Significant difference from pre-intervention.

4.2.3.5. ALCOHOL-RELATED AND OTHER OUTCOMES

There was a significant effect of time for the question "How many AU did you use to drink per occasion over the last month?" [F(2, 14) = 7.801, p=.005]. Pairwise comparisons showed that there was a significant decrease in pre-follow up levels compared to pre-intervention (p<.05).

There was a significant effect of time for the question "How many days do you usually drink alcohol?" [F(2, 14) = 9.800, p<.005]. Pairwise comparisons showed that there was a significant decrease in post-follow up levels compared to pre-intervention (p<.05), and a significant decrease in pre-follow up levels compared to pre-intervention (p<.05).

There was a significant effect of time for the question "How many AU did you drink last week?" [F(2, 14) = 3.742, p<.05]. Pairwise comparisons showed that there was a significant decrease in pre-follow up levels compared to pre-intervention (p<.05). Detailed results are shown in Table 26.

Table 26: Alcohol use questionnaire scores of the subjects that completed the exercise training intervention and follow up.

Question	Pre-intervention	Pre-follow up	Post-follow up

How many AU do you drink per day?	2.500 ± 0.627	1.875 ± 0.549	1.625 ± 0.532
How many AU did you drink last night?	2.625 ± 0.565	2.500 ± 0.886	1.250 ± 0.648
How many times did you consume alcohol over the last month?	6.500 ± 0.378	5.250 ± 0.526	5.125 ± 0.611
How many AU did you use to drink per occasion over the last month?	5.625 ± 0.565	3.813 ± 0.612[2]	4.125 ± 0.515
How many days do you usually drink alcohol?	4.875 ± 0.588	3.750 ± 0.813[1]	3.625 ± 0.783[1]
How many AU did you drink last week?	20.063 ± 3.896	17.125 ± 5.125	14.000 ± 4.683[1]
Would you like to stop drinking alcohol? **(1-10)**	3.625 ± 1.209	4.875 ± 1.246	4.750 ± 1.264
Would you like to cut down on alcohol? **(1-10)**	5.875 ± 1.202	7.000 ± 1.102	6.375 ± 1.085

[1]Significant difference from pre-intervention; [2]Significant difference from pre-follow up.

AU: Alcohol Units (1 AU = 14 grams of pure alcohol). 1: Not much; 10: Very much.

There was a significant effect of time for alcohol units consumed weekly (as recorded by the subjects) [$F(1.227, 8.586) = 5.659$, $p<.05$]. Pairwise comparisons showed that there were significantly decreased ($p<.05$) pre-follow up levels compared to pre-intervention, and a non-significant decrease ($p<.086$) in post-follow up levels compared to pre-intervention.

There was a significant effect of time for IPAQ [$F(2, 14) = 6.284$, $p<.05$]. Pairwise comparisons showed that there were significantly increased ($p<.05$) pre-follow up levels compared to pre-intervention. A significant effect of time was also found for AUDIT [$F(2, 14) = 10.497$, $p<.005$]. Pairwise comparisons showed that there were significantly decreased ($p=.005$) post-follow up levels compared to pre-intervention. Detailed results are shown in Table 27.

Table 27: Alcohol-related and other parameters of the subjects that completed the exercise training intervention and follow up.

Parameter	Pre-intervention	Pre-follow up	Post-follow up
AU consumed over the last week	17.500 ± 3.886	10.625 ± 3.421[1]	5.188 ± 1.458[2]
IPAQ	481.125 ± 160.239	1522.188 ± 304.393[1]	1587.125 ± 445.231
AUDIT	17.375 ± 2.026	13.250 ± 2.596	11.500 ± 1.803[1]
% AUDIT score ≤15	37.5	50	62.5[1]
% AUDIT score >15	62.5	50	37.5[1]

[1]Significant difference from pre-intervention; [2]Non-significant difference from pre-intervention. *AU: Alcohol Units (1 AU = 14 grams of pure alcohol).*

4.3. STUDY 3 (TRIALS OF ACUTE EXERCISE IN HEAVY DRINKERS)

4.3.1. PHYSIOLOGICAL AND ALCOHOL-RELATED OUTCOMES

There was a significant effect of time for mean HR [$F(2, 20) = 7.444$, $p<.005$]. Pairwise comparisons showed that there were significantly decreased ($p<.01$) trial 3 values compared to trial 1.

There was a significant effect of time for time (min) until first drink after trial [$F(1.176, 9.407) = 8.289$, $p<.005$]. Pairwise comparisons showed that there was a significant increase ($p<.05$) in trial 3 values compared to trial 1, a non-significant increase ($p=.084$) in trial 2 values compared to trial 1, and a non-significant increase ($p=.086$) in trial 3 values compared to trial 2.

As regards alcohol units consumed during the week after trial, there were significantly decreased ($p<.05$) trial 3 values compared to trial 1. Alcohol desire did not change during the week after each trial. Resistance, RPM, power and RPE also did not change. Detailed results are shown in Table 28.

Table 28: Physiological and alcohol-related indices before and after 30min-exercise trials throughout exercise training intervention.

Index	Trial 1	Trial 2	Trial 3
Mean Heart Rate	125.636 ± 1.664	121.364 ± 2.513	118.364 ± 2.340[1]
Resistance (kg)	1.435 ± 0.063	1.422 ± 0.068	1.435 ± 0.065
RPM	65.545 ± 1.039	65.909 ± 0.889	65.455 ± 1.371
Power (watts)	94.183 ± 4.667	93.708 ± 4.713	93.929 ± 4.732
RPE	12.700 ± 0.746	11.600 ± 0.521	11.300 ± 0.761
Time until first drink after trial (min)	602.222 ± 98.175	1035.556 ± 230.381[2]	1440.000 ± 338.969[1,3]
How many AU did you drink during the week after trial?	18.636 ± 3.693	15.545 ± 2.125	12.545 ± 2.654[1]
Alcohol desire during the week after trial	7.250 ± 0.559	7.000 ± 0.655	6.625 ± 0.565

[1]Significant difference from trial 1; [2]Non-significant difference from trial 1; [3]Non-significant difference from trial 2. *RPM: Revolutions Per Minute; RPE: Rate of Perceived Exertion; AU: Alcohol Units (1 AU = 14 grams of pure alcohol).*

4.3.2. HEMATOLOGICAL PARAMETERS

No change in MON, LYM%, MON%, MPV and PDW values were observed. There was a significant effect of time for WBC [$F(1, 9) = 28.297$, $p<.001$]. Pairwise comparisons

showed that there were significantly increased (p=.001) post-trial 1 levels compared to pre-trial 1, significantly increased (p=.001) post-trial 2 levels compared to pre-trial 2, and significantly increased (p<.01) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for LYM [F(1, 9) = 14.240, p<.005]. Pairwise comparisons showed that there were significantly increased (p<.005) post-trial 1 levels compared to pre-trial 1, and significantly increased (p<.05) post-trial 2 levels compared to pre-trial 2; however, there was no change in post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for GRA [F(1, 9) = 29.472, p<.001]. Pairwise comparisons showed that there were significantly increased (p<.005) post-trial 1 levels compared to pre-trial 1, significantly increased (p=.001) post-trial 2 levels compared to pre-trial 2, and significantly increased (p=.001) post-trial 3 levels compared to pre-trial 3.

Moreover, there was a significant trial x time interaction for GRA% [F(2, 18) = 3.909, p<.05]. Pairwise comparisons showed only a non-significant increase (p=.066) in post-trial 3 levels compared to pre-trial 3.

A significant effect of time [F(1, 9) = 25.918, p=.001] and trial [F(2, 18) = 14.063, p<.001] for RBCc was found. Pairwise comparisons showed that there were significantly decreased (p=.001) pre-trial 3 levels compared to pre-trial 1, and a non-significant decrease (p=.083) in pre-trial 2 levels compared to pre-trial 1. Moreover, there were significantly decreased (p=.001) post-trial 3 levels compared to post-trial 1, and significantly decreased (p<.05) post-trial 2 levels compared to post-trial 1. Pairwise comparisons also showed that there were significantly increased (p<.01) post-trial 1 levels compared to pre-trial 1, significantly increased (p=.001) post-trial 2 levels compared to pre-trial 2, and significantly increased (p=.001) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time [F(1, 9) = 9.200, p<.05], trial [F(2, 18) = 11.025, p=.001], and a non-significant trial x time interaction [F(2, 18) = 2.809, p=.087] for HGB. Pairwise comparisons showed that there were significantly decreased (p<.05) levels in pre-trial 3 compared to pre-trial 1, and significantly decreased (p<.01) levels in pre-trial 3 compared to pre-trial 2. Moreover, there were significantly decreased (p=.005) levels in post-trial 3 compared to post-trial 1, and significantly decreased (p<.05) levels in post-trial 3 compared to post-trial 2. Pairwise comparisons also showed that there were significantly increased (p<.001) post-trial 3 levels compared to pre-trial 3, and non-significantly increased (p=.059) post-trial 1 levels compared to pre-trial 1.

Furthermore, a significant effect of time for HCT [F(1, 9) = 40.548, p<.001] was found. Pairwise comparisons showed that there were significantly increased (p<.01) levels in post-trial 3 compared to post-trial 2. Pairwise comparisons also showed that there were significantly increased (p=.005) post-trial 1 levels compared to pre-trial 1, significantly increased (p<.005) post-trial 2 levels compared to pre-trial 2, and significantly increased (p<.001) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of trial for MCV [F(2, 18) = 11.259, p=.001]. Pairwise comparisons showed that there were significantly increased (p<.01) levels in pre-trial 3 compared to pre-trial 1, and non-significantly increased (p=.074) levels in pre-trial 2 compared to pre-trial 1. Moreover, there were significantly increased (p=.01) levels in post-trial 3 compared to post-trial 1, and non-significantly increased (p=.064) levels in post-trial 3 compared to post-trial 2.

There was a significant effect of time [F(1, 9) = 19.770, p<.005] and a non-significant effect of trial [F(2, 18) = 2.891, p=.082] for MCH. Pairwise comparisons showed that there was a non-significant decrease (p=.068) in pre-trial 3 levels compared to pre-trial 2, and significantly decreased (p<.05) post-trial 3 levels compared to post-trial 2. Pairwise

comparisons also showed that there were significantly decreased ($p<.05$) post-trial 1 levels compared to pre-trial 1, significantly decreased ($p<.05$) post-trial 2 levels compared to pre-trial 2, and significantly decreased ($p<.05$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time [$F(1, 9) = 13.881$, $p<.005$] and trial [$F(2, 18) = 12.619$, $p<.001$] for MCHC. Pairwise comparisons showed that there were significantly decreased ($p<.01$) levels in pre-trial 3 compared to pre-trial 1, and also significantly decreased ($p<.05$) levels in pre-trial 3 compared to pre-trial 2. Moreover, there were significantly decreased ($p<.01$) levels in post-trial 3 compared to post-trial 1, and also significantly decreased ($p<.001$) levels in post-trial 3 compared to post-trial 2. Pairwise comparisons also showed that there were significantly decreased ($p<.05$) post-trial 1 levels compared to pre-trial 1, significantly decreased ($p<.05$) post-trial 2 levels compared to pre-trial 2, and significantly decreased ($p<.05$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time [$F(1, 9) = 4.904$, $p<.05$] and a significant effect of trial [$F(2, 18) = 5.320$, $p<.05$] for RDW. Pairwise comparisons showed that there were significantly increased ($p<.05$) levels in pre-trial 3 compared to pre-trial 1. Moreover, there were significantly increased ($p<.05$) levels in post-trial 2 compared to post-trial 1. Pairwise comparisons also showed that there were significantly increased ($p<.05$) post-trial 2 levels compared to pre-trial 2.

There was a significant effect of time for PLT [$F(1, 9) = 138.357$, $p<.001$]. Pairwise comparisons showed that there were significantly increased ($p<.005$) post-trial 1 levels compared to pre-trial 1, significantly increased ($p<.001$) post-trial 2 levels compared to pre-trial 2, and significantly increased ($p<.001$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for PCT [$F(1, 8) = 65.606$, $p<.001$]. Pairwise comparisons showed that there were significantly increased ($p<.05$) post-trial 1 levels

compared to pre-trial 1, significantly increased (p<.001) post-trial 2 levels compared to pre-trial 2, and significantly increased (p<.001) post-trial 3 levels compared to pre-trial 3.

Finally, there was a significant effect of trial for ESR [F(1.178, 10.601) = 6.379, p<.05]. Pairwise comparisons showed that there were non-significantly increased (p=.054) levels in pre-trial 3 compared to pre-trial 1, and also significantly increased (p<.05) levels in post-trial 3 compared to post-trial 2. Detailed results are shown in Table 29 and Graphic 1.

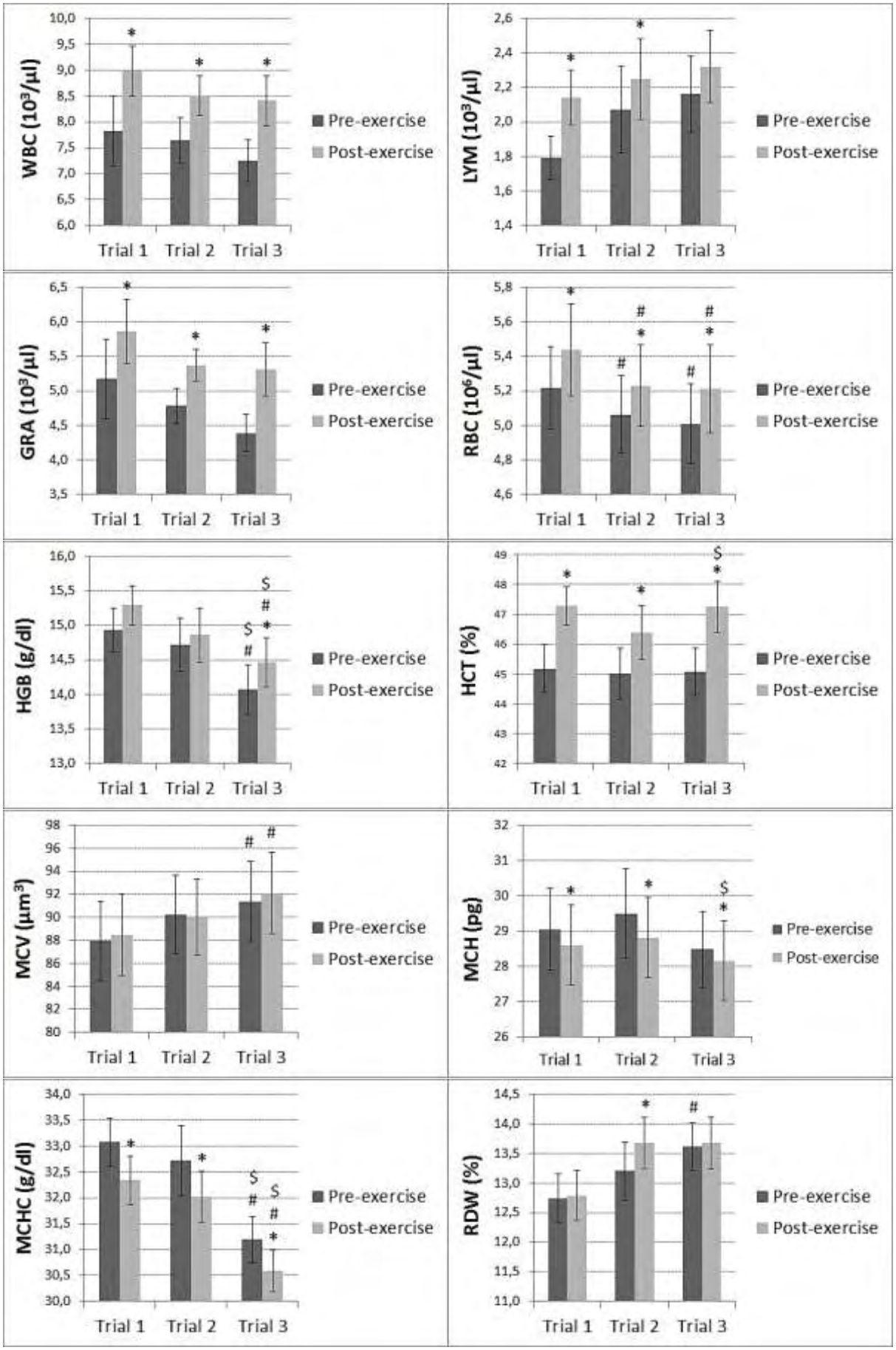
Table 29: CBC and ESR of the subjects before and after 30min-exercise trials throughout exercise training intervention.

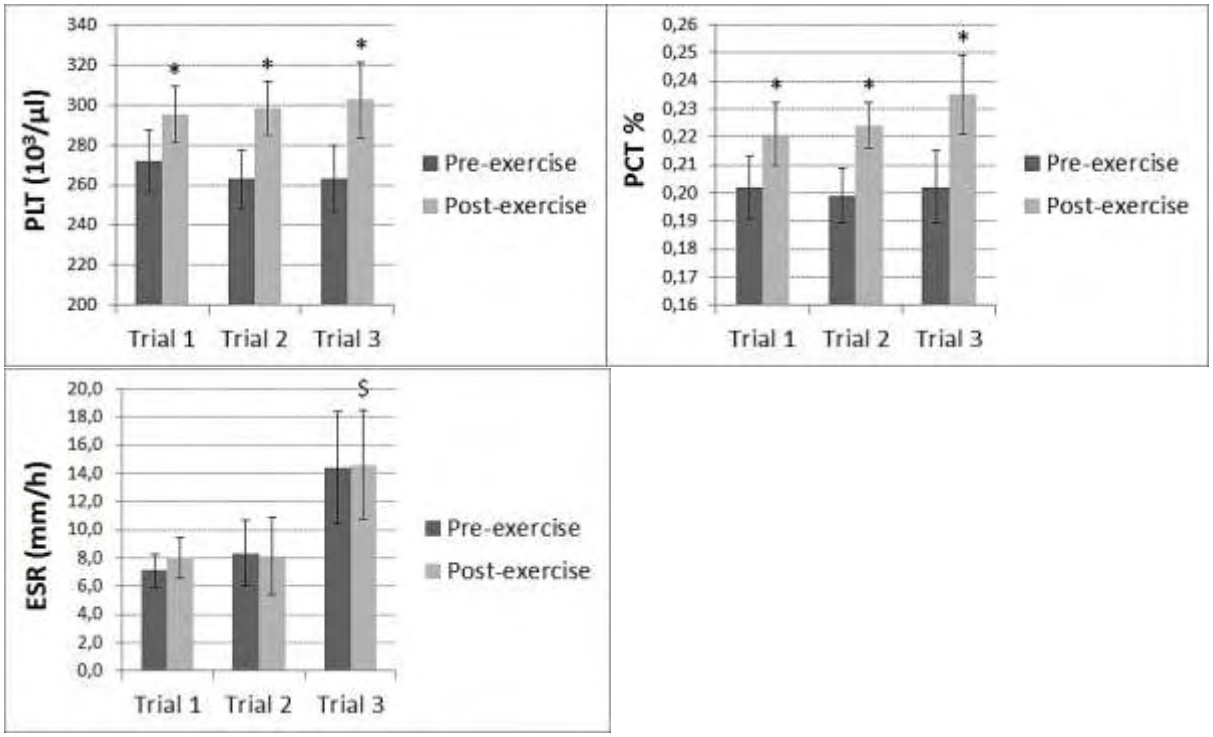
Index	Pre-Trial 1 (Pre-Intervention)	Post-Trial 1 (Pre-Intervention)	Pre-Trial 2 (Mid-Intervention)	Post -Trial 2 (Mid-Intervention)	Pre-Trial 3 (Post-Intervention)	Post-Trial 3 (Post-Intervention)	Normal rage
WBC **(10^3/μl)**	7.820 ± 0.674	8.980 ± 0.482[1]	7.650 ± 0.438	8.500 ± 0.385[2]	7.250 ± 0.401	8.410 ± 0.486[3]	**4.0-12.0**
LYM **(10^3/μl)**	1.790 ± 0.127	2.140 ± 0.159[1]	2.070 ± 0.251	2.250 ± 0.234[2]	2.160 ± 0.221	2.320 ± 0.211	**1.0-5.0**
MON **(10^3/μl)**	0.860 ± 0.122	0.960 ± 0.109	0.820 ± 0.103	0.890 ± 0.102	0.700 ± 0.110	0.780 ± 0.135	**0.1-1.0**
GRA **(10^3/μl)**	5.170 ± 0.583	5.860 ± 0.464[1]	4.780 ± 0.252	5.370 ± 0.224[2]	4.390 ± 0.269	5.310 ± 0.385[3]	**2.0-8.0**
LYM **%**	24.060 ± 2.133	24.640 ± 2.347	26.370 ± 2.126	25.880 ± 1.941	29.570 ± 2.330	27.790 ± 2.348	**25.0-50.0**
MON **%**	10.950 ± 1.000	10.650 ± 0.935	10.870 ± 1.208	10.620 ± 1.207	9.560 ± 1.522	9.320 ± 1.591	**2.0-10.0**
GRA **%**	64.990 ± 64.710	64.710 ± 2.375	62.760 ± 1.689	63.500 ± 1.439	60.870 ± 1.398	62.890 ± 1.647	**50.0-80.0**
RBCc **(10^6/μl)**	5.217 ± 0.239	5.437 ± 0.265[1]	5.063 ± 0.225	5.228 ± 0.236[2]	5.009 ± 0.231[1]	5.213 ± 0.256[3,4]	**4.00-6.20**

HGB **(g/dl)**	14.930 ± 0.321	15.290 ± 0.285	14.720 ± 0.383	14.860 ± 0.391	14.070 ± 0.352[1,2]	14.460 ± 0.353[3,4,5]	**11.0-18.0**
HCT **%**	45.170 ± 0.811	47.280 ± 0.651	45.020 ± 0.852	46.390 ± 0.893	45.080 ± 0.772	47.240 ± 0.852[3,5]	**35.0-55.0**
MCV **(μm^3)**	87.920 ± 3.456	88.450 ± 3.545	90.220 ± 3.440	90.010 ± 3.340	91.360 ± 3.460[1]	92.110 ± 3.569[4]	**80.0-100.0**
MCH **(pg)**	29.050 ± 1.148	28.600 ± 1.133[1]	29.500 ± 1.273	28.810 ± 1.130[2]	28.480 ± 1.084	28.160 ± 1.131[3,5]	**26.0-34.0**
MCHC **(g/dl)**	33.070 ± 0.465	32.340 ± 0.467[1]	32.710 ± 0.678	32.020 ± 0.488[2]	31.190 ± 0.452[1,2]	30.590 ± 0.408[4,5]	**31.0-35.5**
RDW **%**	12.740 ± 0.404	12.790 ± 0.416	13.200 ± 0.480	13.680 ± 0.430[2,4]	13.610 ± 0.396[1]	13.670 ± 0.439	**10.0-16.0**
PLT **(10^3/μl)**	271.700 ± 15.322	295.100 ± 14.052[1]	262.900 ± 14.677	298.400 ± 13.328[2]	263.100 ± 16.498	302.600 ± 18.824[3]	**150-400**
MPV **(μm^3)**	7.656 ± 0.153	7.700 ± 0.181	7.567 ± 0.140	7.589 ± 0.148	7.656 ± 0.159	7.756 ± 0.172	**7.0-11.0**
PCT **%**	0.202 ± 0.011	0.221 ± 0.011[1]	0.199 ± 0.010	0.224 ± 0.008[2]	0.202 ± 0.013	0.235 ± 0.014[3]	**0.200-0.500**
PDW **%**	14.289 ± 0.380	14.678 ± 0.462	14.489 ± 0.423	14.556 ± 0.258	14.056 ± 0.397	14.378 ± 0.381	**10.0-18.0**
ESR **(mm/h)**	7.100 ± 1.197	8.000 ± 1.453	8.350 ± 2.311	8.150 ± 2.741	14.400 ± 3.989	14.600 ± 3.871[5]	**<20**

[1]Significant difference from pre-trial 1; [2]Significant difference from pre-trial 2; [3]Significant difference from pre-trial 3; [4]Significant difference from post-trial 1; [5]Significant difference from post-trial 2.

Graphic 1: CBC and ESR of the subjects before and after 30min-exercise trials throughout exercise training intervention.





*Significant difference from pre-trial at the same group; #Significant difference from trial 1 at the same time-point; $Significant difference from trial 2 at the same time-point.

4.3.3. BIOCHEMICAL PARAMETERS

There was a significant effect of time for LAC [$F(1, 10) = 39.291$, $p<.001$]. Pairwise comparisons showed that there were significantly increased ($p<.001$) post-trial 1 levels compared to pre-trial 1, significantly increased ($p<.001$) post-trial 2 levels compared to pre-trial 2, and significantly increased ($p<.005$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time [$F(1, 9) = 7.044$, $p<.05$] and trial [$F(2, 18) = 6.410$, $p<.01$] for γ-GT. Pairwise comparisons showed that there were significantly decreased ($p<.05$) pre-trial 3 levels compared to pre-trial 1, and significantly decreased ($p<.05$) post-trial 3 levels compared to post-trial 1. Moreover, pairwise comparisons showed that there

were significantly increased ($p<.05$) post-trial 1 levels compared to pre-trial 1, and significantly increased ($p<.05$) post-trial 2 levels compared to pre-trial 2.

There was a significant effect of time for AST [$F(1, 10) = 96.402$, $p<.001$]. Pairwise comparisons showed that there were significantly increased ($p<.005$) post-trial 1 levels compared to pre-trial 1, significantly increased ($p<.001$) post-trial 2 levels compared to pre-trial 2, and significantly increased ($p<.001$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for ALT [$F(1, 8) = 29.599$, $p=.001$]. Pairwise comparisons showed that there were significantly increased ($p<.001$) post-trial 2 levels compared to pre-trial 2, and significantly increased ($p<.001$) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for ACTH [$F(1, 10) = 6.304$, $p<.05$]. Pairwise comparisons showed that there was a significant increase ($p<.05$) in post-trial 1 levels compared to pre-trial 1, and a significant increase ($p<.05$) in post-trial 2 levels compared to pre-trial 2.

There was a significant effect of time for E [$F(1, 10) = 10.270$, $p<.01$]. Pairwise comparisons showed that there were significantly increased ($p<.05$) post-trial 1 levels compared to pre-trial 1, significantly increased ($p<.05$) post-trial 2 levels compared to pre-trial 2, and a non-significant increase ($p=.074$) in post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for NE [$F(1, 10) = 8.573$, $p<.05$] and a non-significant trial x time interaction [$F(2, 20) = 3.027$, $p=.071$]. Pairwise comparisons showed that there were non-significantly decreased ($p=.081$) post-trial 3 levels compared to post-trial 2. Moreover, pairwise comparisons showed that there was a significant increase ($p<.05$) in post-trial 1 levels compared to pre-trial 1, a significant increase

(p<.005) in post-trial 2 levels compared to pre-trial 2, and a non-significant increase (p=.091) in post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for dopamine [F(1, 10) = 29.638, p<.001]. Pairwise comparisons showed that there were significantly increased (p<.05) post-trial 1 levels compared to pre-trial 1, significantly increased (p=.01) post-trial 2 levels compared to pre-trial 2, and non-significantly increased (p=.096) post-trial 3 levels compared to pre-trial 3.

There was a significant effect of time for β-E [F(1, 8) = 17.709, p<.005]. Pairwise comparisons showed that there were significantly increased (p=.01) post-trial 1 levels compared to pre-trial 1, significantly increased (p<.01) post-trial 2 levels compared to pre-trial 2, and significantly increased (p<.05) post-trial 3 levels compared to pre-trial 3. Detailed results are shown in Table 30 and Graphic 2.

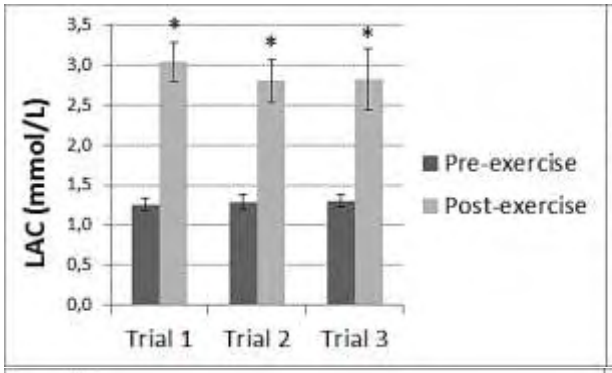
Table 30: Biochemical parameters of the subjects before and after 30min-exercise trials throughout exercise training intervention.

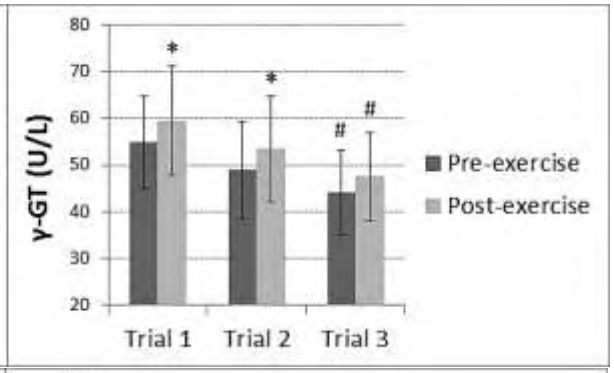
Index	Pre-Trial 1 (Pre-Intervention)	Post-Trial 1 (Pre-Intervention)	Pre-Trial 2 (Mid-Intervention)	Post -Trial 2 (Mid-Intervention)	Pre-Trial 3 (Post-Intervention)	Post-Trial 3 (Post-Intervention)	Normal range
LAC **(mmol/L)**	1.253 ± 0.079	3.041 ± 0.244[1]	1.288 ± 0.094	2.795 ± 0.261[2]	1.304 ± 0.082	2.820 ± 0.388[3]	0.5-2.2 (at rest)
γ-GT **(U/L)**	54.730 ± 10.004	59.520 ± 11.711[1]	48.910 ± 10.276	53.400 ± 11.385[2]	44.070 ± 9.091[1]	47.490 ± 9.510[5]	Men: 11-61; Women: 9-39
AST **(U/L)**	29.245 ± 4.199	43.273 ± 3.178[1]	28.491 ± 2.596	44.982 ± 3.111[2]	30.191 ± 1.955	44.500 ± 3.519[3]	Men: ≤37; Women: ≤31
ALT	28.967 ±	34.656 ±	29.056 ±	38.356 ±	23.267 ±	34.067 ±	Men:

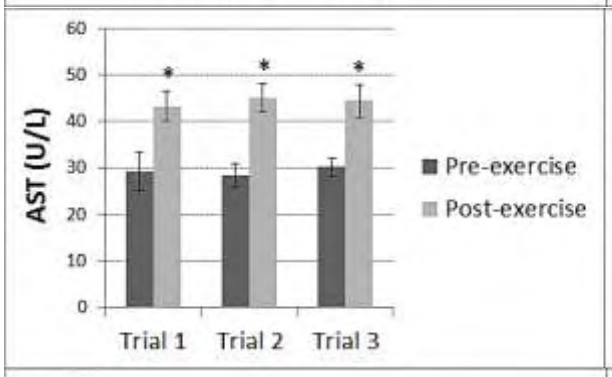
(U/L)	4.382	4.801	3.975	4.768[2]	1.894	3.041[3]	≤42; Women: ≤32
ACTH **(pg/ml)**	30.909 ± 4.015	43.909 ± 5.914[1]	36.091 ± 4.926	47.000 ± 7.844[2]	34.455 ± 4.258	44.000 ± 6.866	10-60 (8-10 a.m.) 6-30 (8-10 p.m.)
E **(pg/ml)**	43.636 ± 3.583	58.636 ± 6.222[1]	42.455 ± 4.543	54.364 ± 6.756[2]	40.818 ± 3.516	48.455 ± 5.585[4]	< 100
NE **(pg/ml)**	275.000 ± 35.006	400.818 ± 78.293[1]	254.364 ± 29.405	476.545 ± 73.394[2]	242.000 ± 28.912	360.000 ± 65.675[4,6]	< 600
Dopamine **(pg/ml)**	39.455 ± 2.644	50.091 ± 4.617[1]	41.182 ± 3.357	58.364 ± 4.749[2]	47.818 ± 6.218	54.636 ± 7.269[4]	< 100
Cortisol **(nM)**	151.100 ± 27.706	162.200 ± 24.131	158.000 ± 18.114	150.600 ± 15.872	167.300 ± 17.692	159.700 ± 15.865	260-720 (morning) 50-350 (evening)
β-E **(pg/ml)**	3.403 ± 0.429	8.489 ± 1.532[1]	4.600 ± 0.713	8.078 ± 1.345[2]	3.748 ± 0.647	8.180 ± 1.695[3]	

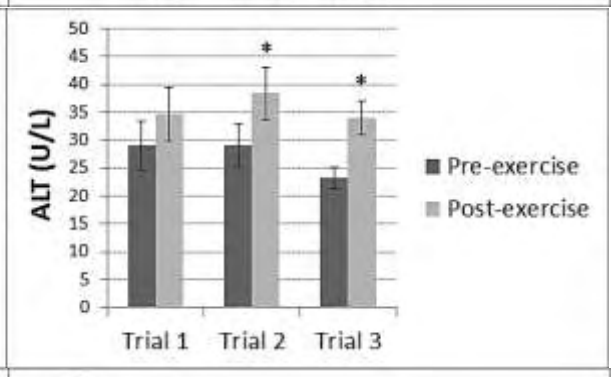
[1]Significant difference from pre-trial 1; [2]Significant difference from pre-trial 2; [3]Significant difference from pre-trial 3; [4]Non-significant difference from pre-trial 3; [5]Significant difference from post-trial 1; [6]Significant difference from post-trial 2.

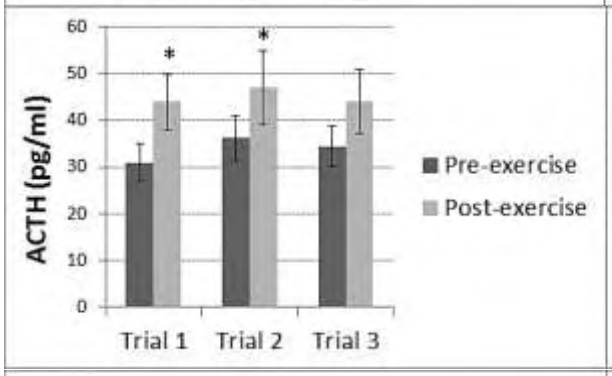
Graphic 2: Biochemical indices of the subjects before and after 30min-exercise trials throughout exercise training intervention.

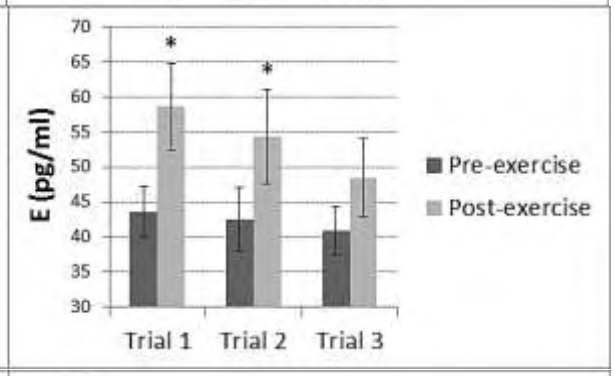


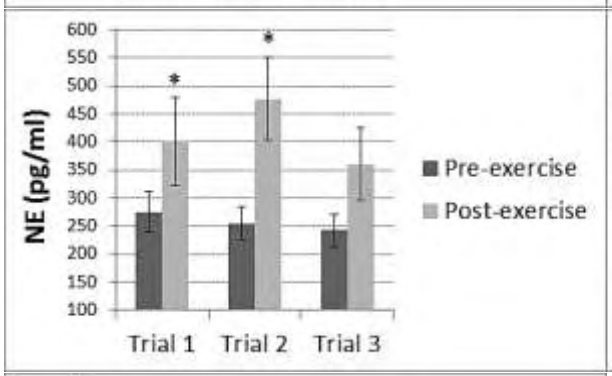


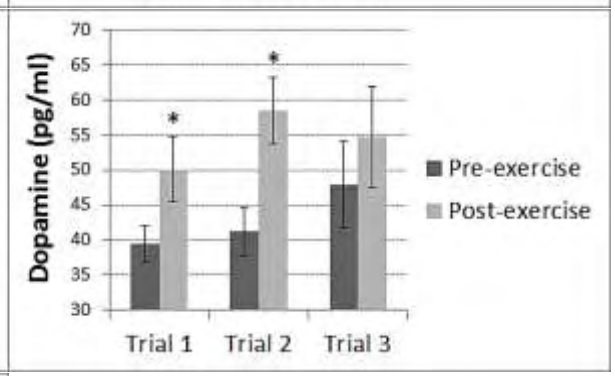


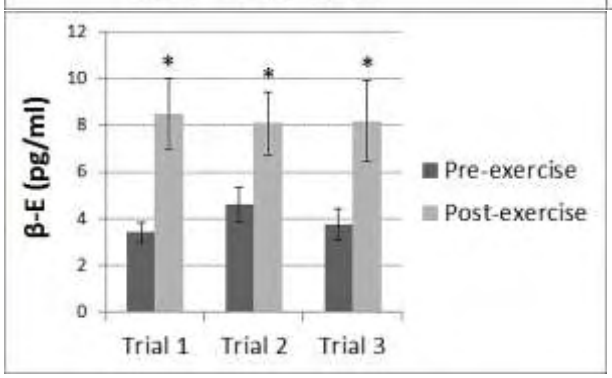












*Significant difference from pre-trial at the same group; #Significant difference from trial 1 at the same time-point; $Significant difference from trial 2 at the same time-point.

4.3.4. MARKERS OF ANTIOXIDANT STATUS

No significant change in bilirubin and UA levels before and after exercise trials throughout training intervention was observed. There was a significant effect of trial [F(2, 20) = 3.872, p<.05] and trial x time [F(2, 20) = 6,757, p<.01] for catalase. Pairwise comparisons showed that there were significantly increased (p<.05) pre-trial 3 levels compared to pre-trial 2. Pairwise comparisons also showed that there were significantly decreased (p<.05) post-trial 3 levels compared to pre-trial 3, and non-significantly increased (p=.094) post-trial 1 levels compared to pre-trial 1 (Graphic 3).

There was a significant effect of trial [F(1.271, 12.708) = 3.700, p<.05] and time [F(1.000, 10.000) = 6.117, p<.05] for TAC. Pairwise comparisons showed that there were significantly increased (p<.01) post-trial 2 levels compared to pre-trial 2 (Graphic 3). Detailed results are shown in Table 31.

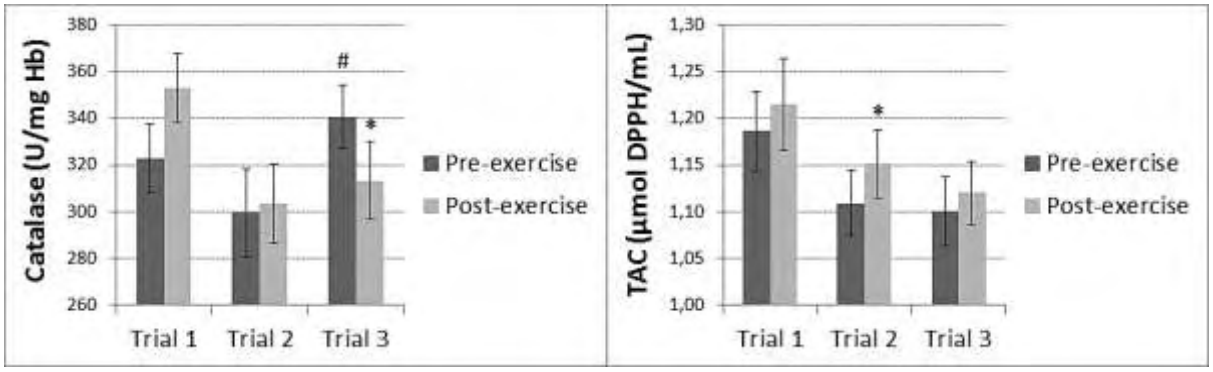
Table 31: Markers of antioxidant status before and after 30min-exercise trials throughout exercise training intervention.

Parameter	Pre-Trial 1	Post-Trial 1	Pre-Trial 2	Post-Trial 2	Pre-Trial 3	Post-Trial 3
Bilirubin **(μmol/L)**	0.649 ± 0.073	0.602 ± 0.048	0.639 ± 0.066	0.647 ± 0.073	0.579 ± 0.050	0.585 ± 0.056
UA **(mg/dl)**	6.427 ± 0.454	6.523 ± 0.463	6.236 ± 0.338	6.341 ± 0.358	6.223 ± 0.321	6.250 ± 0.328
Catalase **(U/mg Hb)**	322.531 ± 14.793	352.960 ± 14.725[1]	299.469 ± 18.690	303.594 ± 16.894	340.735 ± 13.311[2]	313.330 ± 16.589[3]
TAC **(μmol**	1.186 ± 0.043	1.214 ± 0.049	1.109 ± 0.035	1.151 ± 0.036[2]	1.101 ± 0.037	1.120 ± 0.034

DPPH/mL)

[1]Non-significant difference from pre-trial 1; [2]Significant difference from pre-trial 2; [3]Significant difference from pre-trial 3.

Graphic 3: Markers of antioxidant status of the subjects before and after 30min-exercise trials throughout exercise training intervention.



*Significant difference from pre-trial at the same trial; #Significant difference from pre-trial 2.

4.4. STUDY 4 (TRIAL OF ACUTE EXERCISE IN HEAVY DRINKERS Vs CONTROLS)

4.4.1. ANTHROPOMETRIC AND PHYSIOLOGICAL CHARACTERISTICS

Independent t-test revealed that EG had significantly higher ($p<.05$) values of waist and hip circumferences compared to CG.

Table 32: Anthropometric and physiological parameters of the subjects that participated in a trial of acute exercise.

Parameter	EG	CG
Height (cm)	176.855 ± 2.076	177.727 ± 1.349
Weight (kg)	88.846 ± 3.051	84.846 ± 4.193
BMI (kg/m^2)	28.421 ± 0.863	27.028 ± 1.671
SBP	124.182 ± 3.806	119.444 ± 3.610
DBP	82.000 ± 2.569	80.556 ± 3.141
RHR	67.273 ± 2.394	64.636 ± 1.860
Waist	97.446 ± 3.612[1]	86.686 ± 2.084
Hip	104.575 ± 1.333[1]	100.914 ± 0.655
WHR	0.880 ± 0.025	0.859 ± 0.016
Cigarettes/day	11.955 ± 2.746	14.909 ± 3.164

[1]Significant difference from control group.

4.4.2. HEMATOLOGICAL PARAMETERS

No significant change in LYM%, MON%, GRA%, MCV, RDW, PLT, MPV, PCT, PDW and ESR before and after exercise was found in any group. There was a significant effect of time [$F(1, 20) = 24.954$, $p<.001$] for WBC. Pairwise comparisons showed that EG had non-significantly higher ($p=.064$) pre-exercise levels than CG. Pairwise comparisons also showed that there were significantly increased ($p<.01$) post-exercise levels in EG compared to pre-exercise, and significantly increased ($p=.001$) post-exercise levels in CG compared to pre-exercise.

There was a significant effect of time [$F(1, 20) = 30.073$, $p<.001$] for LYM. Pairwise comparisons showed that EG had non-significantly decreased ($p=.067$) pre-exercise levels and significantly decreased ($p<.05$) post-exercise levels compared to CG. Pairwise comparisons also showed that there were significantly increased ($p<.01$) post-exercise levels in EG compared to pre-exercise, and significantly increased ($p<.001$) post-exercise levels in CG compared to pre-exercise.

There was a non-significant effect of time [F(1, 20) = 3.704, p=.069] for MON. Pairwise comparisons showed that EG had significantly increased (p<.05) pre-exercise levels and significantly increased (p<.05) post-exercise levels compared to CG.

There was a significant effect of time [F(1, 20) = 10.507, p<.005] for GRA. Pairwise comparisons showed that EG had significantly increased (p<.05) pre-exercise levels compared to CG. Pairwise comparisons also showed that there were non-significantly increased (p=.069) post-exercise levels in EG compared to pre-exercise, and significantly increased (p<.05) post-exercise levels in CG compared to pre-exercise.

There was a significant effect of time [F(1, 20) = 26.833, p<.001] for RBCc. Pairwise comparisons showed that there were significantly increased (p<.01) post-exercise levels in EG compared to pre-exercise, and significantly increased (p<.001) post-exercise levels in CG compared to pre-exercise.

There was a significant effect of time [F(1, 20) = 16.308, p=.001] for HGB. Pairwise comparisons showed that EG had significantly increased (p<.005) pre-exercise levels and significantly increased (p<.05) post-exercise levels compared to CG. Pairwise comparisons also showed that there were significantly increased (p=.001) post-exercise levels in CG compared to pre-exercise.

There was a significant effect of time [F(1, 20) = 33.009, p<.001] for HCT. Pairwise comparisons showed that EG had significantly increased (p=.01) pre-exercise levels and significantly increased (p<.05) post-exercise levels compared to CG. Pairwise comparisons also showed that there were significantly increased (p<.005) post-exercise levels in EG compared to pre-exercise, and significantly increased (p<.001) post-exercise levels in CG compared to pre-exercise.

There was a significant effect of time [F(1, 20) = 13.582, p<.001] for MCH. Pairwise comparisons showed that there were significantly decreased (p<.005) post-exercise levels in EG compared to pre-exercise.

There was a significant effect of time [F(1, 20) = 13.475, p<.005] for MCHC. Pairwise comparisons showed that there were significantly decreased (p=.001) post-exercise levels in EG compared to pre-exercise. Detailed results are shown in Table 33 and Graphic 4.

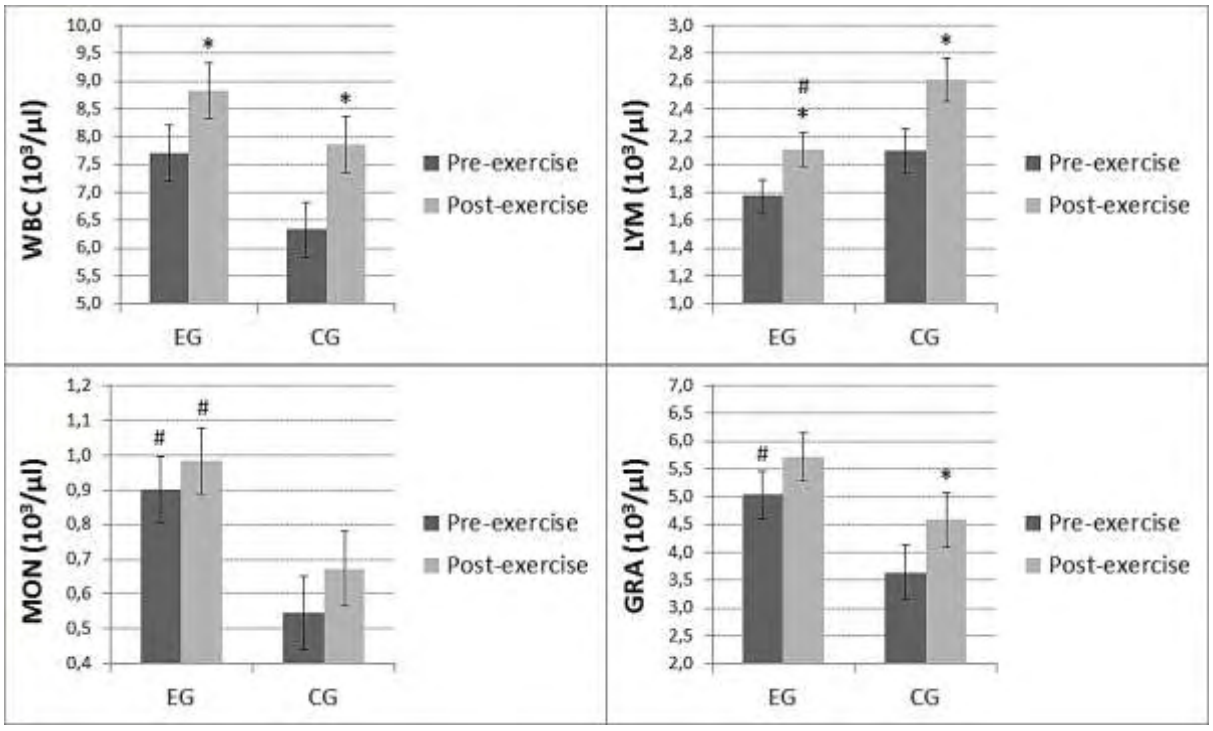
Table 33: Hematological parameters of the subjects that participated in a trial of acute exercise.

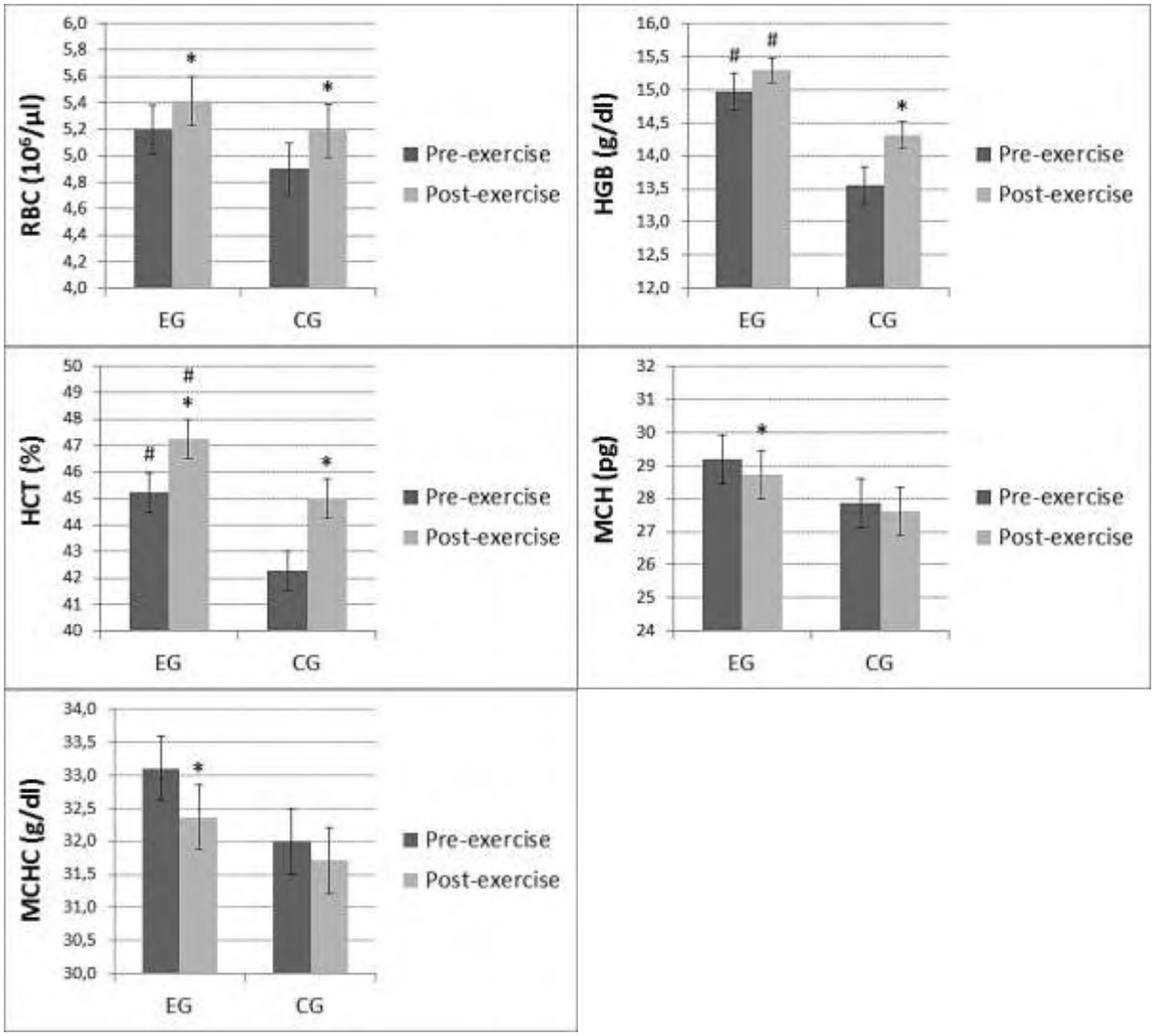
	EG		CG		
Index	**Pre-Trial**	**Post-Trial**	**Pre-Trial**	**Post -Trial**	**Normal rage**
WBC (**10^3/μl)**	7.709 ± 0.499	8.827 ± 0.502[1]	6.327 ± 0.499	7.864 ± 0.502[1]	**4.0-12.0**
LYM (**10^3/μl)**	1.773 ± 0.120	2.109 ± 0.154[1,2]	2.100 ± 0.120	2.609 ± 0.154[1]	**1.0-5.0**
MON (**10^3/μl)**	0.900 ± 0.095[2]	0.982 ± 0.106[2]	0.545 ± 0.095	0.673 ± 0.106	**0.1-1.0**
GRA (**10^3/μl)**	5.036 ± 0.428[2]	5.718 ± 0.496	3.636 ± 0.428	4.582 ± 0.496[1]	**2.0-8.0**
LYM **%**	24.027 ± 1.802	24.673 ± 2.396	32.664 ± 1.802	34.209 ± 2.396	**25.0-50.0**
MON **%**	11.745 ± 1.072	11.127 ± 1.168	8.455 ± 1.072	8.473 ± 1.168	**2.0-10.0**
GRA **%**	64.227 ± 1.929	64.200 ± 2.723	57.691 ± 1.929	56.773 ± 2.723	**50.0-80.0**
RBCc (**10^6/μl)**	5.197 ± 0.182	5.410 ± 0.198[1]	4.899 ± 0.182	5.188 ± 0.198[1]	**4.00-6.20**
HGB (**g/dl)**	14.964 ± 0.279[2]	15.291 ± 0.278[2]	13.545 ± 0.279	14.309 ± 0.278[1]	**11.0-18.0**
HCT **%**	45.227 ± 0.739[2]	47.255 ± 0.742[1,2]	42.264 ± 0.739	45.009 ± 0.742[1]	**35.0-55.0**
MCV **(μm^3)**	88.255 ± 2.744	88.718 ± 2.731	86.600 ± 2.744	87.109 ± 2.731	**80.0-100.0**
MCH **(pg)**	29.191 ± 1.029	28.709 ± 1.018[1]	27.864 ± 1.029	27.618 ± 1.018	**26.0-34.0**
MCHC **(g/dl)**	33.100 ± 0.484	32.364 ± 0.498[1]	32.000 ± 0.484	31.709 ± 0.498	**31.0-35.5**

RDW **%**	12.855 ± 0.430	12.918 ± 0.431	13.027 ± 0.430	13.109 ± 0.431	**10.0-16.0**
PLT (**10^3/μl**)	267.727 ± 12.957	291.909 ± 21.329	267.455 ± 12.957	266.545 ± 21.329	**150-400**
MPV (**μm^3**)	7.791 ± 0.201	7.845 ± 0.195	8.118 ± 0.201	8.164 ± 0.195	**7.0-11.0**
PCT **%**	0.209 ± 0.011	0.230 ± 0.018	0.216 ± 0.011	0.216 ± 0.018	**0.200-0.500**
PDW **%**	14.736 ± 0.479	15.200 ± 0.760	14.936 ± 0.479	13.955 ± 0.760	**10.0-18.0**
ESR **(mm/h)**	6.909 ± 1.253	8.318 ± 1.469	12.286 ± 1.571	11.857 ± 1.842	**<20**

[1]Significant difference from pre-exercise at the same group; [2]Significant difference from control group (CG) at the same time point.

Graphic 4: Hematological parameters of the subjects that participated in a trial of acute exercise.





*Significant difference from pre-exercise at the same group; #Significant difference from control group (CG) at the same time point.

4.4.3. BIOCHEMICAL PARAMETERS

There was a significant effect of time [$F(1, 18) = 66.847$, $p<.001$] for LAC. Pairwise comparisons showed that there were significantly increased ($p<.001$) post-trial levels compared to pre-trial in EG, and significantly increased ($p<.001$) post-trial levels compared to pre-trial in CG.

There was a significant effect of time [F(1, 20) = 4.920, p<.05] and a significant time x group interaction [F(1, 20) = 4.649, p<.05] for γ-GT. Pairwise comparisons showed that there were significantly increased (p<.01) post-trial levels compared to pre-trial in EG.

There was a significant effect of time [F(1, 20) = 41.200, p<.001] for AST. Pairwise comparisons showed that there were significantly increased (p<.001) post-trial levels compared to pre-trial in EG, and significantly increased (p=.001) post-trial levels compared to pre-trial in CG.

Pairwise comparisons showed that there were significantly increased (p<.05) post-trial levels compared to pre-trial in EG for ALT.

There was a significant effect of time [F(1, 20) = 10.335, p<.005] for ACTH. Pairwise comparisons showed that there were significantly increased (p<.05) post-trial levels compared to pre-trial in EG, and non-significantly increased (p=.07) post-trial levels compared to pre-trial in CG.

There was a significant effect of time [F(1, 20) = 13.585, p=.001] for E. Pairwise comparisons showed that there were significantly increased (p<.005) post-trial levels compared to pre-trial in EG.

There was a significant effect of time [F(1, 20) = 13.980, p=.001] for NE. Pairwise comparisons showed that there were non-significantly increased (p=.084) post-trial levels compared to pre-trial in EG, and significantly increased (p<.005) post-trial levels compared to pre-trial in CG.

There was a significant effect of time [F(1, 20) = 27.817, p<.001] for dopamine. Pairwise comparisons showed that there were significantly increased (p=.001) post-trial levels compared to pre-trial in EG, and significantly increased (p=.001) post-trial levels compared to pre-trial in CG.

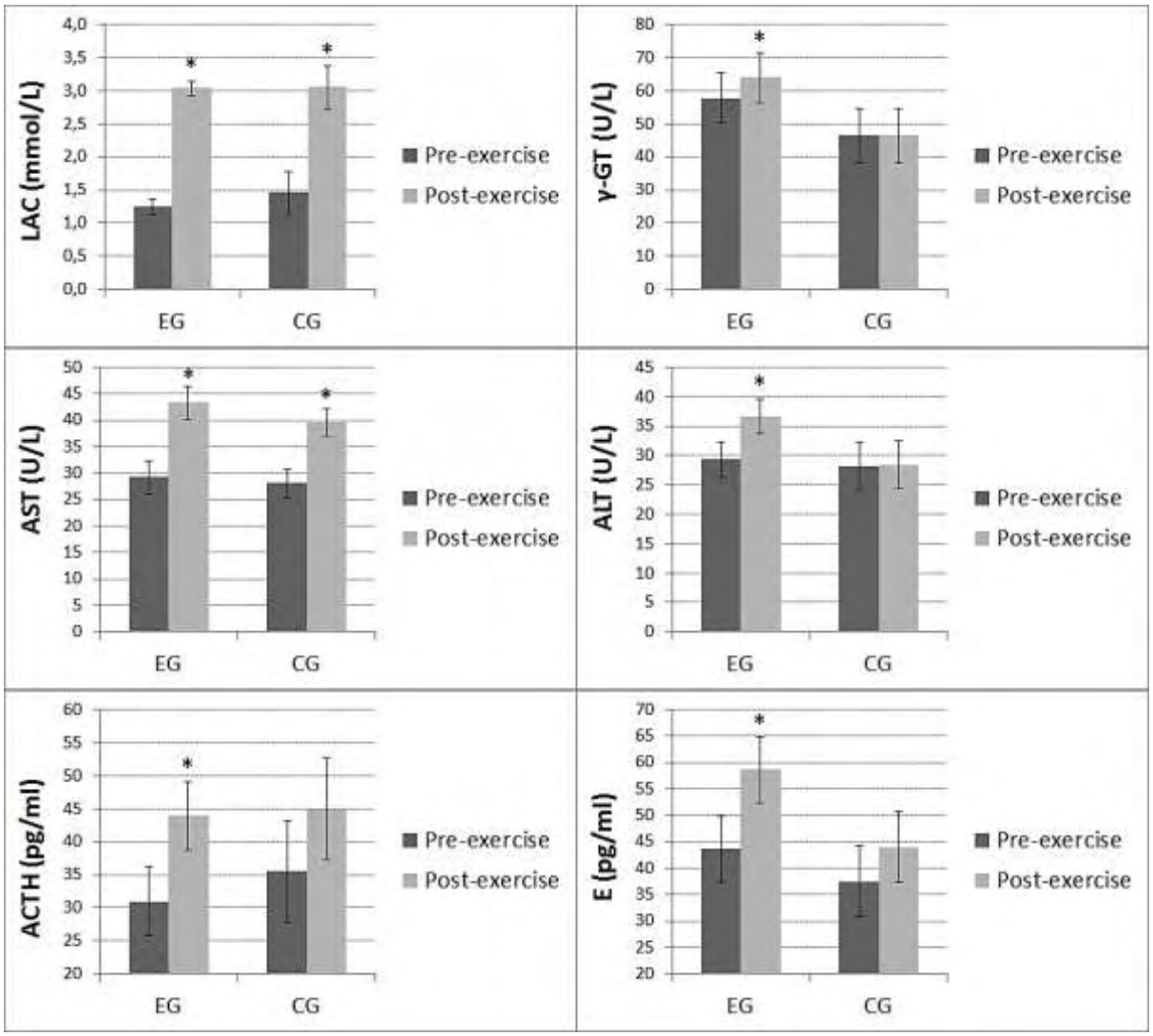
There was a significant effect of time [F(1, 16) = 13.885, p<.005] and a significant time x group interaction [F(1, 16) = 8.201, p<.05] for β-E. Pairwise comparisons showed that there were non-significantly lower (p=.078) post-trial levels in EG compared to post-trial levels in CG. Pairwise comparisons also showed that there were significantly increased (p<.001) post-trial levels compared to pre-trial in EG. Detailed results are shown in Graphic 4.

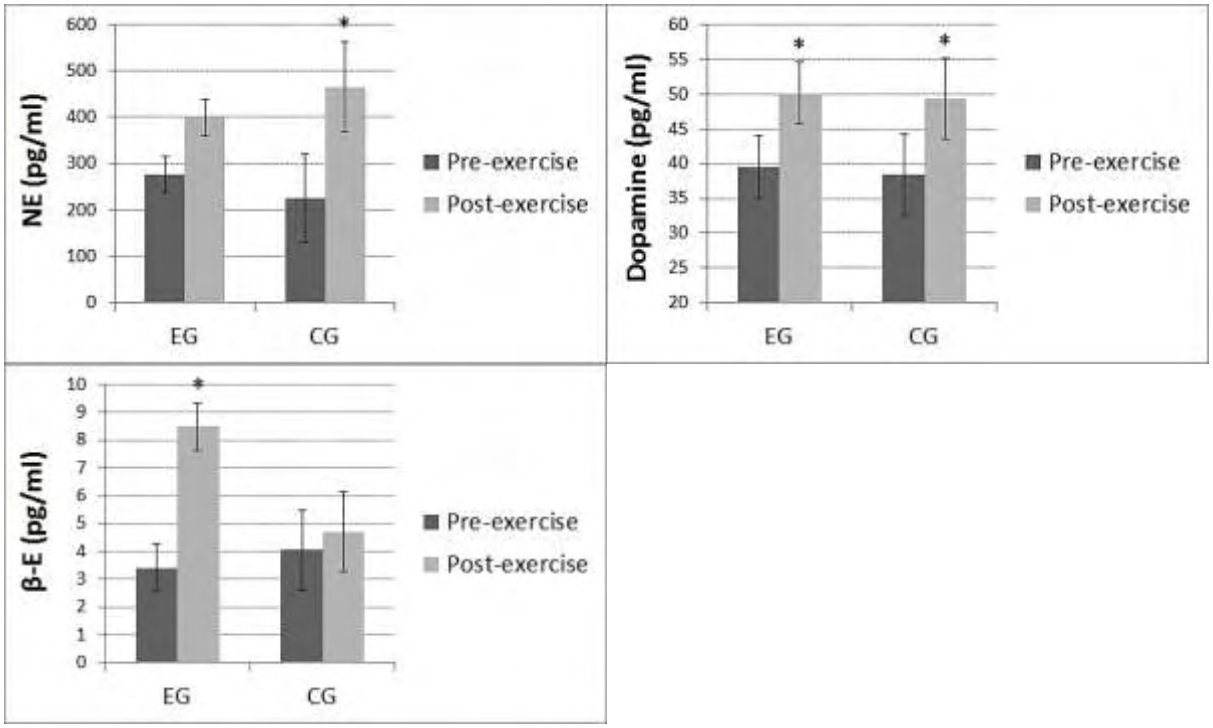
Table 34: Biochemical parameters of the subjects that participated in a trial of acute exercise.

Index	EG		CG		Normal range
	Pre-Trial	**Post-Trial**	**Pre-Trial**	**Post-Trial**	
LAC **(mmol/L)**	1.253 ± 0.105	3.041 ± 0.314[1]	1.466 ± 0.116	3.058 ± 0.347[1]	0.5-2.2 (at rest)
γ-GT **(U/L)**	59.741 ± 7.454	63.914 ± 8.243[1]	46.414 ± 7.454	46.473 ± 8.243	Men: 11-61; Women: 9-39
AST **(U/L)**	29.245 ± 3.144	43.273 ± 2.616[1]	28.064 ± 3.144	39.536 ± 2.616[1]	Men: ≤37; Women: ≤31
ALT **(U/L)**	29.273 ± 2.940	36.609 ± 3.999[1]	28.200 ± 2.940	28.400 ± 3.999	Men: ≤42; Women: ≤32
ACTH **(pg/ml)**	30.909 ± 5.177	43.909 ± 7.679[1]	35.455 ± 5.177	44.909 ± 7.679[2]	10-60 (8-10 a.m.) 6-30 (8-10 p.m.)
E **(pg/ml)**	43.636 ± 6.309	58.636 ± 6.744[1]	37.455 ± 6.309	44.000 ± 6.744	< 100
NE **(pg/ml)**	275.000 ± 38.952	400.818 ± 96.291[2]	224.909 ± 38.952	464.727 ± 96.291[1]	< 600
Dopamine **(pg/ml)**	39.455 ± 4.507	50.091 ± 5.804[1]	38.455 ± 4.507	49.273 ± 5.804[1]	< 100
Cortisol **(nM)**	161.545 ± 21.683	167.455 ± 18.720	168.000 ± 21.683	182.727 ± 18.720	260-720 (morning) 50-350 (evening)
β-E **(pg/ml)**	3.403 ± 0.849	8.489 ± 1.418[1,3]	4.048 ± 0.849	4.713 ± 1.418	

[1]Significant difference from pre-trial at the same group; [2]Non-significant difference from pre-trial at the same group; [3]Non-significant difference from control group at the same time point.

Graphic 5: Biochemical parameters of the subjects that participated in a trial of acute exercise.





*Significant difference from pre-trial at the same group.

4.4.4. MARKERS OF ANTIOXIDANT STATUS

There was a significant effect of time [F(1, 20) = 6.129, p<.05] for catalase. Pairwise comparisons showed that there were significantly increased (p<.05) post-trial levels compared to pre-trial in EG.

There was a significant effect of time [F(1, 20) = 7.090, p<.05] for TAC. Pairwise comparisons showed that there were significantly increased (p<.01) post-trial levels compared to pre-trial in CG.

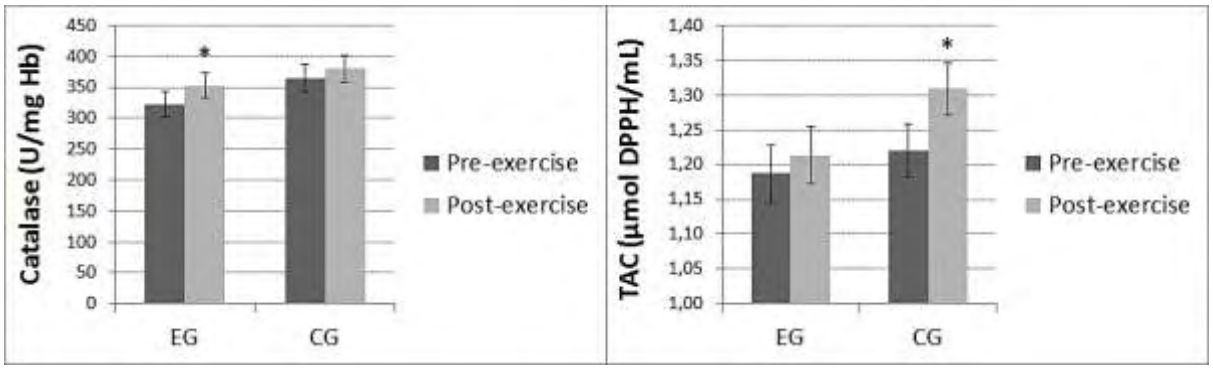
Table 35: Markers of antioxidant status of the subjects that participated in a trial of acute exercise.

Parameter	EG		CG	
	Pre-Trial 1	**Post-Trial 1**	**Pre-Trial 1**	**Post-Trial 1**

Bilirubin **(μmol/L)**	0.649 ± 0.078	0.626 ± 0.101	0.629 ± 0.078	0.666 ± 0.101
UA **(mg/dl)**	6.427 ± 0.463	6.523 ± 0.477	6.191 ± 0.463	6.245 ± 0.477
Catalase **(U/mg Hb)**	322.531 ± 20.462	352.960 ± 21.900[1]	364.718 ± 20.462	379.488 ± 21.900
TAC **(μmol DPPH/mL)**	1.187 ± 0.041	1.213 ± 0.038	1.220 ± 0.041	1.309 ± 0.038[1]

[1]Significant difference from pre-trial at the same group.

Graphic 6: Markers of antioxidant status of the subjects that participated in a trial of acute exercise.



*Significant difference from pre-trial at the same group.

5. DISCUSSION

Research on the effects of exercise on alcohol urge and other alcohol use related outcomes in individuals with AUDs is limited. The purpose of the present dissertation was to add knowledge on the effects of exercise on alcohol urge and other alcohol use related outcomes in individuals with AUDs as well as to investigate for the first time the possible physiological mechanisms involved.

5.1. PHYSIOLOGICAL PARAMETERS

The 8-week ET intervention led to improvement in several indices of fitness in heavy drinkers. Some fitness gains were also observed in seven previous studies (Gary & Guthrie, 1972; Sinyor et al., 1982; Weber, 1984; Murphy et al., 1986; Donaghy, 1997; Ermalinski, 1997; Brown et al., 2009), while one study (Palmer et al., 1988) did not find significant changes in fitness.

More specifically, the 8-week ET intervention had a positive effect on body composition as indicated by changes in body weight, BMI and waist circumference. Heavy drinkers that participated in the 8-week ET intervention had increased waist circumference compared to controls at the baseline, and the ET intervention led to increased physical activity levels along with decreased weight, BMI and waist circumference. It is well known that exercise training contributes to weight control and leads to beneficial metabolic changes in both healthy and non-healthy populations. Regarding individuals with AUDs, only Brown et al. (2009) have previously reported reduced body fat percentage after ET intervention.

Moreover, no effect of ET intervention on blood pressure was observed. Only two previous studies have examined changes in blood pressure and provided inconsistent results. One study reported decreased systolic blood pressure (Ermalinski et al., 1997)

while the other one did not detect any changes (Lehofer et al., 1995). One possible explanation for this result is that blood pressure of heavy drinkers that participated in the ET intervention was within the normal limits at the baseline and only a slight decrease could be obtained after intervention.

Results on the effect of ET intervention on parameters of physical functioning are mixed. Physical activity level, flexibility and sit-ups increased, while no significant change in VO_2max, 4min HR, handgrip and push-ups after exercise intervention were observed. Literature also provides inconsistent evidence regarding physical functioning after ET intervention. No changes in VO_2max after ET intervention was also found by another study (Palmer et al., 1988), while most studies have reported a significant positive effect of exercise on VO2max (Sinyor et al., 1982; Donaghy, 1997; Capodaglio et al., 2003; Brown et al., 2014). Regarding muscular strength, two previous studies have reported that it was significantly increased in their intervention groups (Donaghy, 1997; Capodaglio et al., 2003). It is possible that combination of aerobic with resistant exercise could lead to greater changes in parameters of physical functioning, especially in those related to muscle strength.

Physical activity levels were 3 times higher after 8 weeks of ET intervention compared to baseline, and they stayed at these levels after 4 weeks of follow up. This is in agreement with previous studies where increased levels of physical activity were achieved and maintained up to 6 months after intervention (Donaghy, 1997; Capodaglio et al., 2003; Brown et al., 2014).

All these favorable physiological outcomes in combination with a decrease in alcohol consumption lead to the suggestion that exercise is beneficial for heavy drinkers and highlight the importance of ET intervention for the treatment of AUDs.

5.2. HEMATOLOGICAL PARAMETERS

Immune response to exercise and its association with pathological conditions is not well understood yet due to numerous factors involved. Although no change in WBC types was found in alcoholics after acute exercise of low intensity, a significant increase in WBC and LYM after acute exercise of moderate intensity was observed in heavy drinkers. Therefore, it is likely that immune response to exercise was associated with exercise intensity. Indeed, the immune response of the human body to acute exercise depends on the intensity, duration, and mode of exercise. In general, bouts of prolonged, high-intensity exercise have been linked to greater immune response than bouts of acute exercise of moderate duration (less than 60 min) and intensity (less than 60% VO2max) (Nieman, 1997). Since moderate intensity but not low intensity exercise was able to cause an immune response, it could be hypothesized that moderate intensity exercise is more suitable for a long-term intervention in order to achieve adaptations in individuals with AUDs. Indeed, the 8-week ET intervention resulted in adaptations as indicated by an increase in flexibility and number of sit ups, without causing any change in the levels of WBC types. These results suggest that aerobic exercise of moderate intensity is safe and effective for individuals with AUDs.

The studies of the present dissertation showed that acute exercise of both low and moderate intensity led to significant increased levels of RBCc and Hct in alcoholics and heavy drinkers. These results indicate that exercise may have resulted in plasma volume loss due to fluid shifting towards the surrounding interstitial spaces and water loss from the body (increased sweating and water vapor loss from the respiratory tract). The amount of decreased plasma volume and dehydration mainly depends on the intensity of the exercise. The present results showed that individuals with AUDs may be more prone to dehydration after exercise. However, it could be explained by the fact that participants were not

instructed to drink water before, during or immediately after exercise. Therefore, it is recommended that individuals with AUDs consume fluids during exercise in order to maintain fluid homeostasis.

Furthermore, the 8-week ET intervention led to decreased levels of RBCc, Hb, MCH, MCHC and increased levels of MCV and RDW in heavy drinkers. Individuals who drink heavily often experience malnutrition either due to their eating habits (e.g., alcohol contains “empty calories”, meaning that it has no nutrition value) or due to the negative effect of alcohol on absorption, digestion, and usage of essential nutrients (Morgan, 1982). However, no clinical manifestation of anemia and malnutrition was evident, since the levels of these RBC indices were within the normal ranges.

5.3. BIOCHEMICAL PARAMETERS

- HPA axis

Acute exposure to alcohol seems to lead to a fast and transient increase in β-E release by the pituitary and hypothalamus (Keith et al., 1986; Thiagarajan et al., 1989) in a dose dependent manner (Gianoulakis, 1990). On the other hand, chronic heavy exposure to alcohol may lead to decreased synthesis and release of β-E in the hypothalamus and pituitary as well as lower density and activity of the opioid receptors that may be responsible for some feelings of discomfort and negative reinforcement (increased craving and motivation to consume ethanol) (Gianoulakis, 2004). However, various studies on the effect of chronic ethanol administration on the pituitary and hypothalamic β-E systems have provided very inconsistent results due to methodological problems (Gianoulakis, 2004).

Concerning β-E levels at rest, it was found that alcoholics had lower baseline β-E levels compared to control group, whereas baseline β-E levels in heavy drinkers were not significantly different from those in control group. These results indicate that there may be a central β-E deficiency in alcoholics but not in heavy drinkers. Central β-E deficiency in human alcoholics has been previously shown to occur in animal models (Genazzani et al., 1982; Gianoulakis, 2004), and may contribute to increased alcohol urge and relapse rates observed in these individuals (Gianoulakis, 2004). The effects of alcohol on the body mainly depend on the amount consumed, the pattern of drinking and the duration of exposure. However, it must be taken into consideration that in the present dissertation only male heavy drinkers were included, whereas gender differences in β-E levels at rest may exist. Previous reports have demonstrated that female heavy drinkers have lower plasma β-E and ACTH levels than male heavy drinkers (Gianoulakis et al., 2003). In addition to that, genetic factor may also contribute to β-E levels at rest. Individuals with a family history of alcoholism have shown to exhibit lower plasma β-E (Dai et al., 2002a; Gianoulakis et al., 1996) and ACTH (Dai et al., 2002b; Waltman et al., 1998) than those with no family history of alcoholism. Since there was no report of family history of alcoholism among heavy drinkers that participated in the present dissertation, this could explain the failure to observe differences in their baseline levels of β-E and ACTH compared to control group.

After acute exercise of low intensity, β-E levels increased significantly only in alcoholics and approached those of the control group. Moreover, a 17% non-significant alcohol urge reduction in alcoholics was reported. After acute exercise of moderate intensity, β-E levels increased significantly only in heavy drinkers and were twice as high in heavy drinkers as in control group. These results suggest that even 30 minutes of low intensity exercise in alcoholics and 30 minutes of moderate intensity exercise in heavy drinkers can affect the opioid system's activity. Therefore, exercise of greater intensity and duration could cause

an even greater effect on opioid system activity, which in turn could result in significantly decreased alcohol urge. It has been suggested that exercise-induced increase in β-E levels may improve mood and reduce alcohol urge in individuals with AUDs (Zourbanos et al., 2011), and the results from this study partially support this hypothesis.

Moreover, the 8-week ET intervention showed that there was a 29.2% non-significant increase in β-E levels at the 4th week of ET intervention; however, β-E levels decreased again reaching the baseline levels at the 8th week of ET intervention. Although acute exercise seems to affect opioid system in both heavy drinkers and alcoholics, chronic exercise of moderate intensity may only lead to medium-term increases in β-E. This could be explained by the fact that heavy drinkers may not experience a central β-E deficiency and, therefore, ET intervention cannot have a great effect on opioid system.

Interestingly, heavy drinkers reported that their desire for alcohol was high and their will to cut down on alcohol consumption was low throughout ET intervention, whereas their alcohol consumption significantly decreased at the end of ET intervention. It would be expected that a decrease in alcohol consumption would be accompanied by a reduction in desire for alcohol or/and that heavy drinkers would be determined to cut down on alcohol; however, that was not the case. It is possible that other physiological or psychological factors may have contributed to these unexpected findings.

Changes in the levels of HPA axis hormones can reflect changes in the function of central nervous system (CNS). Resting ACTH, E, NE, dopamine and cortisol levels did not differ between heavy drinkers and control group. After acute exercise of moderate intensity, ACTH, E, NE and dopamine levels increased and cortisol levels did not significantly change in heavy drinkers and control group. It has been observed that changes in cortisol levels depend on exercise intensity; an increase in cortisol levels is usually reported during high-intensity exercise (> 60% VO2max). The moderate intensity of exercise used in the

present study protocols could explain the failure to detect significant changes in cortisol levels after acute exercise.

Moreover, the 8-week ET intervention had no effect on any of those indices in heavy drinkers at rest; however, responses to acute exercise at the 8th week of ET intervention were lower than before training. Indeed, it is known that the sympathetic nervous system plays an important role in mediating the response to exercise in healthy individuals (van Euler & Hellner, 1952; Vendsalu, 1960). Abnormal response of sympathetic nervous system both at rest and during physical exercise indicates abnormal cardiac response, something that was not evident in heavy drinkers. It is suggested that ET intervention may resulted in physical adaptations caused by alteration in the sympathetic nervous system of heavy drinkers.

The responses of HPA axis hormones to exercise had not been examined in alcoholics. Alcohol dependence has been reported to cause changes in HPA axis in the CNS of alcohol-dependent subjects (Adinoff et al., 1991; Bruijnzeel and Gold, 2005; Hundt et al., 2001; Inder et al., 1995; Wand and Dobs, 1991). In a study by Coiro and colleagues (2007), a deficient activation of the HPA axis with a non-significant ACTH/cortisol increase after exercise in alcohol-dependent individuals were reported after 4 weeks of abstinence. Interestingly, ACTH/cortisol response to exercise was back to normal after 8 weeks of abstinence, indicating that the period of abstinence from alcohol may affect the activation of the HPA axis during exercise. Thus, it cannot be suggested that there is a deficient activation of the HPA axis during exercise in heavy drinkers that are not alcohol-dependent, because they may not experience great alterations in the function of CNS.

- Liver function

γ-GT is an indicator of liver function and elevated levels are usually observed in liver malfunction or problems with the bile ducts. Chronic excessive exposure to alcohol can result in liver inflammation which in turn can impair liver function. Thus, changes in γ-GT levels can reflect changes in alcohol drinking pattern. AST and ALT are commonly used as indicators of liver inflammation and viral infections. More specifically, increased AST levels are mainly attributable to muscular inflammation, while increased ALT levels most commonly indicate liver inflammation (Banfi et al., 2012). Heavy drinkers that participated in the studies had non-significantly greater baseline γ-GT levels compared to controls, possibly due to heavy drinking. Cigarette smoking is another factor that can result in increased γ-GT levels, independently of alcohol use pattern (Nieman, 1997). For that reason, controls that were selected to participate in the study had the same smoking habits with heavy drinkers. Therefore, it is more likely that alcohol intake was the main factor that influenced the non-significantly increased γ-GT levels in heavy drinkers compared to controls. This is also suggested by the observation that the 8-week ET intervention led to decreased γ-GT levels along with reduced alcohol intake in heavy drinkers. Moreover, baseline levels of AST and ALT were within the normal limits and did not change after ET intervention. It has been suggested that central adiposity is positively associated with liver enzyme levels independently from BMI, which may be the result of unrecognized fatty liver (Stranges et al., 2004b). Obese individuals may be at greater risk of developing fatty liver than heavy drinkers; however, individuals with both increased body mass and heavy alcohol drinking may be at even greater risk of developing this condition (Bellentani et al., 2000). Heavy drinkers were overweight (BMI = 28.421 ± 0.863) but their WHR was within the normal limits, and these characteristics were similar with those of the control

group. Thus it could be hypothesized that changes in liver enzyme could reflect changes in the amounts of alcohol consumed.

Concerning liver enzyme responses to acute exercise, γ-GT and ALT levels increased significantly in heavy drinkers but not in control group, while AST levels increased in both groups after exercise. Exercise is known to cause a transient increase in liver enzymes in healthy individuals and the extent of that increase is dependent on the intensity, duration and type of exercise (Halonen & Konttinen, 1962; Parikh & Ramanathan, 1977). The results indicate that heavy drinkers may be more prone to increased liver inflammation after acute exercise of moderate intensity due to increased oxidative stress. However, no negative effect on liver enzymes was observed after 8 weeks of ET intervention, indicating that moderate intensity aerobic ET is safe for heavy drinkers and it can positively affect their γ-GT levels.

Another finding that leads to the conclusion that exercise is safe for heavy drinkers is that total bilirubin levels were within normal limits and did not change after acute exercise or ET intervention. Increased total bilirubin at rest is an indicator of various problems of liver function; however, increased total bilirubin levels after intense exercise is a normal finding in healthy individuals that is caused by hemolysis. Thus it can be concluded that acute and chronic exercise of moderate intensity did not cause hemolysis in heavy drinkers.

5.4. EFFECTIVENESS OF THE EXERCISE TRAINING INTERVENTION

The study on the effects of long-term exercise in heavy drinkers involved an 8-week supervised aerobic ET intervention with exercise sessions of increasing frequency and duration; a minimum of two 30-min supervised exercise sessions per week was set. Previous studies involved three to sixteen weeks of ET intervention of mostly aerobic

exercise (55%–85% of HRmax), one to five times per week (Gary & Guthrie, 1972; McKelvy et al., 1980; Sinyor et al., 1982; Weber, 1984; Murphy et al., 1986; Palmer et al., 1988; Donaghy, 1997; Brown et al., 2009; Brown et al., 2014). In contrast to other studies that used a standard protocol for all subjects, in this study subjects were motivated to increase the frequency and duration of exercise sessions as part of long-term lifestyle modifications that include increased physical activity and reduced alcohol consumption (before each session they were asked to set a goal for exercise duration and alcohol consumption). That means that individuals were free to decide which exercise duration and frequency was the more suitable and pleasant for them, in order to increase the possibility of achieving these long-term lifestyle modifications. Heart rate was monitored during exercise sessions and it was shown that all subjects were exercising at moderate intensity (50-60%) throughout the ET intervention.

The Alcohol Use Disorders Identification Test (AUDIT - Moussas et al., 2009) was used in order to identify heavy drinkers with AUDs. Before intervention, 36.4% of heavy drinkers had a score of > 8 and ≤ 15 which indicates hazardous drinking, 27.3% of heavy drinkers had a score of ≥ 16 and ≤ 19 which indicates harmful drinking, and 36.4% of heavy drinkers had a score of ≥ 20 which indicates serious abuse/addiction (total AUDIT score: 17.455 ± 1.603). After ET intervention, AUDIT scores and weekly alcohol consumption significantly decreased, while the levels of physical activity (IPAQ) significantly increased. The subjects that participated in the follow up maintained increased physical activity levels, and low AUDIT scores and weekly alcohol consumption. In addition to that, desire for alcohol, which plays an important role in the treatment of AUD, was also significantly decreased after exercise intervention. Since alcohol consumption was recorded throughout the study by the subjects, the results could be inaccurate. For that reason, changes in γ-GT levels, which reflect changes in alcohol

consumption, were examined. It was found that changes in γ-GT levels were in accordance with changes in alcohol consumption. Indeed, γ-GT levels also decreased after 8 weeks of exercise and, therefore, it is likely that self-reported alcohol consumption was in agreement with the actual amounts of alcohol consumed. All these results indicate that the 8-week supervised ET intervention achieved the goal of long-term lifestyle modifications for the majority of subjects.

Subjects were recording their daily alcohol consumption during control condition and ET intervention. There were no changes in alcohol consumption during control whereas gradually decreased alcohol consumption was reported throughout ET intervention. Therefore, the fact that subjects had to record their alcohol consumption did not affect their behavior towards alcohol. Moreover, subjects that participated in ET intervention were aware of their drinking problem and it could be hypothesized that they would make an effort to cut down on alcohol consumption anyway. However, their intention to quit or cut down on alcohol was medium and did not change after 8 weeks of ET intervention. Taken all these together, it is suggested that decreased alcohol consumption was the result of ET intervention.

Alcohol-related outcomes are very important in the treatment of AUD as they provide useful information on the efficacy of interventions aimed at alcohol abuse cessation. In the literature, only five studies have examined alcohol-related parameters after exercise such as alcohol urge, abstinence rates and drinking behavior through questionnaires and/or via biochemical parameters, with positive outcomes observed (Sinyor et al., 1982; Ermalinski et al., 1997; Ussher et al., 2004; Brown et al., 2009; Brown et al., 2014). Both physiological and psychological mechanisms may contribute to these positive effects of exercise. Physiological mechanisms were previously described.

During the 8-week ET intervention, 21.4% of subjects dropped out. This drop-out rate is lower in comparison to findings from previous studies that reported 43.5% drop-out rate during a 16-week ET intervention (Weber, 1984) and 26% during a 4-week ET intervention (Donaghy, 1997). Moreover, the remaining subjects successfully completed the ET intervention with a drop-out rate of 27.3% after 4 weeks of follow up. Subjects who completed 4 weeks of follow up reported unchanged levels of physical activity, alcohol consumption and AUDIT scores. Subjects that dropped out after 4 weeks of follow up claimed they had a lack of free time, and the data obtained via telephone communication were not included as they could be inaccurate. Moreover, the rate of subjects who maintained a physical active lifestyle (61.5%) one month after completion of ET intervention was much higher than that previously reported. Donaghy (1997) showed that only 35% of the subjects sustained a homebased, non-supervised exercise program 2 months after supervised ET intervention, with an additional drop-out rate of 65% after 2 months and another 17% after 5 months of follow up. These findings also suggest that the 8-week ET intervention conducted in the present study was effective in helping most of the subjects increase their physical activity and maintain increased levels for at least another month.

6. CONCLUSIONS AND FUTURE DIRECTIONS

This is the first study to investigate the acute and long-term effects of exercise on physiological, biochemical and alcohol-related parameters in heavy drinkers. Although the results indicate that the 8-week ET intervention was effective in reducing alcohol consumption and increasing physical activity, there were some limitations. First of all, the number of subjects was small and there was a lack of control group in the 8-week ET intervention; however, there was a control condition before intervention in which subjects were recording their alcohol consumption and physical activity. No difference in any variable tested was observed after 4 weeks of no intervention (control condition), indicating that the findings of this study were associated with the 8-week ET intervention. Randomized controlled studies with a larger number of subjects could provide more reliable results.

Since only male heavy drinkers were included, findings of the ET intervention cannot be generalized for female heavy drinkers. Women are more vulnerable to the effects of alcohol consumption than men due to physiological differences. Moreover, gender differences may also influence the effects of exercise on AUDs. Recently, it has been shown that voluntary exercise resulted in decreased ethanol consumption and preference in female but not in male mice, indicating that there may be gender differences in the efficacy of voluntary exercise and its effects on alcohol-related behaviours (Gallego et al., 2015).

Furthermore, biochemical indices from other tissues than blood could offer a better understanding of the physiological mechanisms that involve in individuals with AUDs who participate in ET interventions. Direct measurement of β-E and other endogenous opioids in the living human brain is not possible, while indirect measurements in the plasma may not reflect the levels of endogenous opioid levels in the brain. Nevertheless, there are some speculations that the levels of endogenous opioids in the plasma may act

centrally and, therefore, reflect changes in central nervous system activity (Biddle & Mutrie, 1991). Longer duration of follow up would lead to a better conclusion about the long-term effectiveness of an ET intervention.

In summary, it is suggested that an 8-week supervised aerobic ET intervention may be beneficial for individuals with AUDs in many aspects of health. Although only a small number of studies on the effects of exercise on alcohol consumption in individuals with AUDs exist, the limited available data indicate that this is a promising research topic. ET interventions that include motivation goals may be more effective in achieving and maintain lifestyle modifications in individuals with AUDs than only exercise or psychological support. Future studies with a larger number of subjects that would also examine gender differences should be conducted.

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APPENDIX A

Ethics approval received from the University of Thessaly review board

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΤΜΗΜΑ ΕΠΙΣΤΗΜΗΣ ΦΥΣΙΚΗΣ ΑΓΩΓΗΣ ΚΑΙ ΑΘΛΗΤΙΣΜΟΥ

Εσωτερική Επιτροπή Δεοντολογίας

Τρίκαλα: 12/12/2012
Αριθμ. Πρωτ.:653

Αίτηση Εξέτασης της πρότασης για διεξαγωγή Έρευνας με τίτλο: «Άσκηση, κάπνισμα & αλκοόλ: διερεύνηση μηχανισμών και παρεμβάσεις για διακοπή, πρόληψη και ευαισθητοποίηση»

Επιστημονικώς υπεύθυνος-η / επιβλέπων-ουσα: Θεοδωράκης Ιωάννης
Ιδιότητα: Καθηγητής Αθλητικής Ψυχολογίας
Ίδρυμα: Πανεπιστήμιο Θεσσαλίας
Τμήμα: Επιστήμης Φυσικής Αγωγής και Αθλητισμού

Κύριος ερευνητής-τρια / φοιτητής-τρια: Γεωργακούλη Καλλιόπη
Πρόγραμμα Σπουδών: Διδακτορικός Κύκλος Σπουδών
Ίδρυμα: Πανεπιστήμιο Θεσσαλίας
Τμήμα: Επιστήμης Φυσικής Αγωγής και Αθλητισμού

Κύριος ερευνητής-τρια / φοιτητής-τρια: Τζατζάκη Θεοδώρα
Πρόγραμμα Σπουδών: Διδακτορικός Κύκλος Σπουδών
Ίδρυμα: Πανεπιστήμιο Θεσσαλίας
Τμήμα: Επιστήμης Φυσικής Αγωγής και Αθλητισμού

Κύριος ερευνητής-τρια / φοιτητής-τρια: Τσιάμη Αναστασία
Πρόγραμμα Σπουδών: Διδακτορικός Κύκλος Σπουδών
Ίδρυμα: Πανεπιστήμιο Θεσσαλίας
Τμήμα: Επιστήμης Φυσικής Αγωγής και Αθλητισμού

Η προτεινόμενη έρευνα θα είναι:

Ερευνητικό πρόγραμμα **X** Μεταπτυχιακή διατριβή ☐ Διπλωματική εργασία ☐ Ανεξάρτητη έρευνα ☐

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Η Εσωτερική Επιτροπή Δεοντολογίας του Τ.Ε.Φ.Α.Α., Πανεπιστημίου Θεσσαλίας μετά την υπ. Αριθμ. 6-1/12-12-2012 συνεδρίασή της εγκρίνει τη διεξαγωγή της προτεινόμενης έρευνας.

Ο Πρόεδρος της
Εσωτερικής Επιτροπής
Δεοντολογίας – ΤΕΦΑΑ

APPENDIX B

Consent form for participation in the study

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ-ΤΕΦΑΑ

Συναίνεση δοκιμαζόμενου

1. Σκοπός της ερευνητικής εργασίας

Σκοπός αυτής της εργασίας είναι να μελετηθούν επιδράσεις της άσκησης πάνω σε διάφορους αιματολογικούς, βιοχημικούς και φυσιολογικούς παράγοντες σε άτομα που καταναλώνουν αλκοόλ.

2. Διαδικασία μετρήσεων

Θα χρειαστεί να έρθεις στο εργαστήριο Βιοχημείας του ΤΕΦΑΑ 5 φορές. Στην πρώτη επίσκεψή σου στο εργαστήριο θα συμπληρώσεις ένα ερωτηματολόγιο υγείας και φυσιολογικής δραστηριότητας. Ακόμα, θα συμπληρώσεις ένα ερωτηματολόγιο σχετικά με τις συνήθειες κατανάλωσης αλκοόλ. Όλες οι επισκέψεις σου θα γίνουν πρωινές ώρες, θα είσαι νηστικός και θα απέχεις από το κάπνισμα, το φαγητό και το αλκοόλ για 12 ώρες ώστε να γίνουν οι αιμοληψίες. Επίσης θα γίνονται και οι ανθρωπομετρικές μετρήσεις (ύψος, βάρος, ποσοστό σωματικού λίπους, περιφέρειες), η αξιολόγηση της φυσικής κατάστασης και η μέτρηση της αρτηριακής πίεσης. Μετά την δεύτερη επίσκεψη στο εργαστήριο θα ξεκινήσει το πρόγραμμα άσκησης υπό την επίβλεψη ενός ειδικού καθηγητή φυσικής αγωγής, το οποίο θα διαρκέσει 8 εβδομάδες.

3. Κίνδυνοι και ενοχλήσεις

Αιμοληψία. Θα χρησιμοποιηθεί μία μικρή βελόνα σύριγγας για τη λήψη φλεβικού από τη μεσοβασιλική φλέβα. Υπάρχει πιθανότητα μικρού μώλωπα στο σημείο της αιμοληψίας ενώ μπορεί να αισθανθείς πόνο κατά τη διάρκεια της αιμοληψίας και ζαλάδα ή τάσεις λιποθυμίας τόσο κατά τη διάρκεια όσο και μετά από την αιμοληψία. Σε κάθε δείγμα η συνολική ποσότητα αίματος που θα ληφθεί από έμπειρο γιατρό θα είναι 20ml η οποία δεν θα έχει απολύτως καμία αρνητική συνέπεια.

4. Προσδοκώμενες ωφέλειες

Τα ευρήματα από την εργασία θα σου δώσουν την δυνατότητα να καταλάβεις εάν και κατά πόσον η άσκηση έχει θετικές επιδράσεις στον ανθρώπινο οργανισμό ατόμων που κάνουν συχνή κατανάλωση αλκοόλ.

5. Δημοσίευση δεδομένων – αποτελεσμάτων

Η συμμετοχή σου στην έρευνα συνεπάγεται ότι συμφωνείς με τη δημοσίευση των δεδομένων και των αποτελεσμάτων της, με την προϋπόθεση ότι οι πληροφορίες θα είναι ανώνυμες και δε θα αποκαλυφθούν τα ονόματα των συμμετεχόντων. Τα δεδομένα που θα συγκεντρωθούν θα κωδικοποιηθούν με αριθμό, ώστε το όνομα σου δε θα φαίνεται πουθενά.

6. Πληροφορίες

Μη διστάσεις να κάνεις ερωτήσεις γύρω από το σκοπό, τον τρόπο πραγματοποίησης της εργασίας ή τον υπολογισμό της λειτουργικής σου ικανότητας. Αν έχεις κάποιες αμφιβολίες ή ερωτήσεις, ζήτησέ μας να σου δώσουμε πρόσθετες εξηγήσεις.

7. Ελευθερία συναίνεσης

Η άδειά σου να συμμετάσχεις στην εργασία είναι εθελοντική. Είσαι ελεύθερος να μην συναινέσεις ή να διακόψεις τη συμμετοχή σου όποτε επιθυμείς.

Διάβασα το έντυπο αυτό και κατανοώ τις διαδικασίες που θα εκτελέσω. Συναινώ να συμμετέχω στην εργασία.

Ημερομηνία: __/__/__

Ονοματεπώνυμο και υπογραφή συμμετέχοντος	Ονοματεπώνυμο και υπογραφή παρατηρητή	Υπογραφή ερευνητή

APPENDIX C

Health Record Questionnaire

Ερωτηματολόγιο υγείας

Όνομα.....

Ημερομηνία.....

Παρακαλώ συμπληρώστε

Έχετε κάποιο πρόβλημα υγείας για το οποίο

Α) είστε υπό φαρμακευτική αγωγή ναι [ ] όχι [ ]

Β) είστε υπό ιατρική παρακολούθηση ναι [ ] όχι [ ]

Τα τελευταία 2 χρόνια, εξαιτίας κάποιας ασθένειας

Α) επισκεφτήκατε το γιατρό σας ναι [ ] όχι [ ]

Β) επισκεφτήκατε εξωτερικά ιατρεία ναι [ ] όχι [ ]

Γ) μείνατε στο νοσοκομείο ναι [ ] όχι [ ]

Είχατε ποτέ κάποια από τις παρακάτω καταστάσεις;

Α) Επιληψία ναι [ ] όχι [ ]

Β) Έκζεμα ναι [ ] όχι [ ]

Γ) Διαβήτης ναι [ ] όχι [ ]

Δ) Άσθμα ναι [ ] όχι [ ]

Ε) Καρδιαγγειακά νοσήματα ναι [ ] όχι [ ]

Ζ) Πεπτικά προβλήματα ναι [ ] όχι [ ]

Η) Προβλήματα γυναικολογικά ναι [ ] όχι [ ]

Θ) Προβλήματα οστών και αρθρώσεων ναι [ ] όχι [ ]

Ι) Προβλήματα ισορροπίας και συναρμογής ναι [ ] όχι [ ]

Κ) Προβλήματα όρασης/ ακοής ναι [ ] όχι [ ]

Λ) Προβλήματα θυρεοειδούς ναι [ ] όχι [ ]

Μ) Ορμονικά προβλήματα ναι [ ] όχι [ ]

Ν) Προβλήματα ήπατος και νεφρών ναι [ ] όχι [ ]

Ξ) Μούδιασμα άκρων ναι [ ] όχι [ ]

Ο) Άλλα προβλήματα ναι [ ] όχι [ ]

Αν είστε γυναίκα

Α) σχεδιάζετε να μείνετε έγκυος ναι [ ] όχι [ ]

Β) είστε η νομίζετε ότι είστε έγκυος ναι [ ] όχι [ ]

Γ) παίρνετε χάπια αντισύλληψης ή ορμόνες ναι [ ] όχι [ ]

Δ) είστε στην εμμηνόπαυση ναι [ ] όχι [ ]

Κάποιος από τους συγγενείς πρώτου βαθμού είχε

Α) Καρδιαγγειακά προβλήματα ναι [ ] όχι [ ]

Β) Διαβήτη ναι [ ] όχι [ ]

Γ) Εγκεφαλικό ναι [ ] όχι [ ]

Δ) Κάποια άλλη ασθένεια ναι [ ] όχι [ ]

Καπνίζετε αυτή την περίοδο ναι [ ] όχι [ ]

Έχετε καπνίσει ποτέ ναι [ ] όχι [ ]

Αν ναι, για πόσο καιρό κα πότε το κόψατε.....

Πόσες μονάδες αλκοόλ πίνετε σε μια εβδομάδα.....

Γυμνάζεστε ναι [ ] όχι [ ]

Πόσες φορές την εβδομάδα.....

Αναφέρετε το είδος γυμναστικής.....

Αν απαντήσατε ναι σε κάποια από τις ερωτήσεις, παρακαλώ περιγράψτε εν συντομία

.....
.....
.....
.....
.....

☐ Δηλώνω ότι είμαι σωματικά υγιής και δεν πάσχω από κάποια πάθηση, βλάβη, ασθένεια ή αναπηρία που θα μπορούσε να εμποδίσει τη συμμετοχή μου στην πειραματική διαδικασία.

☐ Αναγνωρίζω ότι έχω εξετασθεί και ο γιατρός μου έχει δώσει την άδεια να συμμετάσχω, ή έχω αποφασίσει να συμμετάσχω στην πειραματική διαδικασία χωρίς την έγκριση του γιατρού μου. Αναλαμβάνω κάθε ευθύνη για την συμμετοχή μου.

Ημ/νία Υπογραφή ερευνητή Υπογραφή συμμετέχοντα

APPENDIX D

International Physical Activity Questionnaire (IPAQ)

Παρακάτω ακολουθούν ερωτήσεις σχετικά με την άσκηση που κάνεις στον ελεύθερο χρόνο σου

Σκέψου το χρόνο που αφιέρωσες στο διάστημα των τελευταίων 7 ημερών για να ασκηθείς στον ελεύθερο χρόνο σου. Σκέψου μόνο τις φορές που έκανες άσκηση για τουλάχιστον 10 λεπτά κάθε φορά.

1. Κατά τη διάρκεια των τελευταίων 7 ημερών, πόσες ημέρες έκανες στον ελεύθερο χρόνο σου άσκηση υψηλής έντασης (ανέπνεες πολύ πιο δύσκολα από ότι συνήθως), όπως προπόνηση με βάρη, γρήγορη ποδηλασία, τρέξιμο, αθλοπαιδιές (π.χ., ποδόσφαιρο, μπάσκετ)

_____ ημέρες ανά εβδομάδα

□ Καμία έντονη άσκηση → προχωρήστε στην ερώτηση 3

2. Πόσο χρόνο συνήθως αφιέρωσες για να κάνεις άσκηση υψηλής έντασης σε μία από αυτές τις ημέρες;

_____ ώρες την ημέρα

_____ λεπτά την ημέρα

3. Κατά τη διάρκεια των τελευταίων 7 ημερών, πόσες μέρες έκανες στον ελεύθερο χρόνο σου άσκηση μέτριας έντασης (ανέπνεες λίγο πιο δύσκολα από ότι συνήθως), όπως κολύμπι, ποδηλασία σε κανονικό ρυθμό, γρήγορο περπάτημα. Σκέψου μόνο τις φορές που έκανες άσκηση για τουλάχιστον 10 λεπτά. Μην συμπεριλάβεις το περπάτημα.

_____ ημέρες ανά εβδομάδα

□ Καμία άσκηση μέτριας έντασης → προχωρήστε στην ερώτηση 5

4. Πόσο χρόνο συνήθως αφιέρωσες για να κάνεις άσκηση μέτριας έντασης σε μία από αυτές τις ημέρες;

___ώρες την ημέρα

_____ λεπτά την ημέρα

□ Δεν γνωρίζω/ Δεν είμαι σίγουρος/η

5. Κατά τη διάρκεια των τελευταίων 7 ημερών, πόσες ημέρες έκανες στον ελεύθερο χρόνο σου περπάτημα για τουλάχιστον 10 λεπτά;

_____ ημέρες ανά εβδομάδα

□ Καθόλου περπάτημα

6. Πόσο χρόνο συνήθως αφιέρωσες περπατώντας σε μία από αυτές τις ημέρες;

_____ ώρες την ημέρα

_____ λεπτά την ημέρα

□ Δεν γνωρίζω/ Δεν είμαι σίγουρος/η

7. Πόσο χρόνο καθόσουν σε μία από αυτές τις ημέρες;

_____ ώρες την ημέρα

_____ λεπτά την ημέρα

□ Δεν γνωρίζω/ Δεν είμαι σίγουρος/η

APPENDIX E

Alcohol Use Disorders Identification Test (AUDIT)

ΗΛΙΚΙΑ: _____ ΦΥΛΟ: _____
ΕΠΑΓΓΕΛΜΑ: _____ ΟΙΚΟΓ. ΚΑΤΑΣΤΑΣΗ: _____

ΔΙΑΓΝΩΣΤΙΚΗ ΔΟΚΙΜΑΣΙΑ ΔΙΑΤΑΡΑΧΗΣ ΧΡΗΣΗΣ ΑΛΚΟΟΛ					
Παρουσιάστε αυτή τη δομημένη συνέντευξη,					
ενημερώνοντας τον ασθενή ότι θα του κάνετε ερωτήσεις για την χρήση των αλκοολούχων ποτών τον προηγούμενο χρόνο.					
Βάλτε έναν κύκλο σε αυτό που προσεγγίζει καλύτερα την απάντηση του ασθενούς					
1. Πόσο συχνά πίνετε κάτι που περιέχει αλκοόλ					
(0)	Ποτέ	(1) Μια φορά το μήνα ή λιγότερο	(2) 2 με 4 φορές το μήνα	(3) 2-3 φορές την εβδομάδα	(4) 4 ή περισσότερες φορές την εβδομάδα
2. Πόσα αλκοολούχα ποτά καταναλώνετε μια συνηθισμένη μέρα όταν πίνετε					
(0)	1 ή 2	(1) 3 ή 4	(2) 5 ή 6	(3) 7 με 9	(4) 10 ή περισσότερες
3. Πόσο συχνά πίνετε 6 ή περισσότερα ποτά την ημέρα					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
4. Πόσο συχνά τον τελευταίο χρόνο διαπιστώνετε ότι δεν είστε σε θέση να σταματήσετε να πίνετε άπα και αρχίσατε					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
5. Πόσο συχνά τον τελευταίο χρόνο δεν καταφέρατε να κάνετε αυτό που οι άλλοι περίμεναν από σας λόγω του ότι είχατε πιει					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
6. Πόσο συχνά, μέσα στον τελευταίο χρόνο, χρειάστηκε να πιείτε ένα ποτό το πρωί για να μπορέσετε να λειτουργήσετε μετά από ένα βράδυ που είχατε πιει πολύ					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
7. Πόσο συχνά, μέσα στον τελευταίο χρόνο, είχατε αισθήματα τύψεων και ενοχής μετά που είχατε πιει πολύ					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
8. Πόσο συχνά μέσα στον τελευταίο χρόνο, δεν μπορούσατε να θυμηθείτε τι συνέβη το προηγούμενο βράδυ γιατί είχατε πιει					
(0)	Ποτέ	(1) Λιγότερο από 1 φορά το μήνα	(2) Τουλάχιστον μία φορά το μήνα	(3) Τουλάχιστον μία φορά την εβδομάδα	(4) Καθημερινά ή σχεδόν καθημερινά
9. Έχει τύχει εσείς ή κάποιος άλλος να τραυματισθεί λόγω του ότι είχατε πιει					
(0)	Όχι	(2) Ναι, αλλά όλα τον τελευταίο χρόνο		(4) Ναι, πέρυσι	
10. Υπάρχει κάποιος συγγενής, φίλος ή γιατρός ή που έχει ανησυχήσει για το πόσο πίνετε ή σας έχει συστήσει να το κόψετε					
(0)	Όχι	(2) Ναι, αλλά όλα τον τελευταίο χρόνο		(4) Ναι, πέρυσι	

APPENDIX F

Questionnaire for Alcohol Intake (QAI)

<u>Παρακάτω ακολουθούν ερωτήσεις σχετικά με τη χρήση του αλκοόλ</u>

(υπολόγισε σαν ποτό: 1 μπύρα 330ml, 1 ποτήρι κρασί 150 ml , μισή μερίδα ουίσκι 50 ml, τζιν, βότκα, κτλ.)

Πόσα ποτά πίνεις συνήθως τη μέρα?	( )
Πόσα ποτά ήπιες χθες?	( )

1. Τον περασμένο μήνα πόσες φορές ήπιες κάποιο αλκοολούχο ποτό;							
1	2	3	4	5	6	7	8
Δεν ήπια καθόλου αλκοόλ τον περασμένο μήνα	Ήπια μια φορά τον περασμένο μήνα	Ήπια 2-3 φορές τον περασμένο μήνα	Ήπια 1 ή 2 φορές την εβδομάδα	Ήπια 3 ή 4 φορές την εβδομάδα	Ήπια 5 ή 6 φορές την εβδομάδα	Έπινα σχεδόν κάθε μέρα	Έπινα κάθε μέρα

2. Τον περασμένο μήνα πόσα αλκοολούχα ποτά συνήθως κατανάλωνες κάθε φορά που έπινες;							
1	2	3	4	5	6	7	8
Δεν ήπια καθόλου αλκοόλ τον περασμένο μήνα	1 ποτό	2 ποτά	3 ποτά	4 ποτά	5 ποτά	6 ποτά	7 ή και περισσότερα ποτά

3. Συνήθως, πόσες μέρες την εβδομάδα πίνεις κάποιο αλκοολούχο ποτό;_____

4. Πόσα αλκοολούχα ποτά πίνεις συνήθως την εβδομάδα;_____

5. Μπορείς να θυμηθείς πόσο αλκοόλ ήπιες την προηγούμενη εβδομάδα;

(π.χ. 6 μπύρες, 4 ποτά, 4 ποτήρια κρασί, 3 σφηνάκια)

APPENDIX G

Alcohol Urge Questionnaire (AUQ)

Επιθυμείς να διακόψεις τη χρήση αλκοόλ;

Καθόλου Πάρα πολύ

0 1 2 3 4 5 6 7 8 9 10

Επιθυμείς να περιορίσεις τη χρήση αλκοόλ;

Καθόλου Πάρα πολύ

0 1 2 3 4 5 6 7 8 9 10