Molecular & Applied Physiology

Therapeutic Exercise

THESIS

EFFECTS OF LIFESTYLE INTERVENTION IN TYPE 2 DIABETES:

A CASE STUDY AND REVIEW OF THE LITERATURE

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INTRODUCTION

I. Physiology of Insulin Secretion and Action

Secretion

Insulin is secreted by the pancreatic β-cells, in response to glucose, amino acids and fatty acids, in order to regulate their metabolism (oxidation or storage) in the liver and peripheral tissues (such as skeletal muscle and adipose tissue). Glucose is the most important of the three, since it is used by cells of all tissues (especially the Central Nervous System) as a major energy fuel. Therefore, it is of the utmost importance that its levels in the circulation are maintained within a narrow physiological range (70-180mg/dl). The β-cells respond to glucose in a couple of ways:

Primarily, in the fasting state, when the plasma levels of glucose are low (70-100mg/dl), the β-cells respond with a low (continuous) rate of secretion (basal insulinemia). This is important for maintaining euglycemia during sleep at night as well as between meals during the day.

Secondly, in the postprandial state, the β-cells respond within minutes to the increase in the levels of glucose in blood by increasing insulin secretion accordingly (early or first-phase insulin secretion). The speed by which β-cells respond to glucose postprandially is critical for the physiological regulation of metabolism. Primarily, it contributes to the necessary conditions for the oxidation of glucose in the tissues, therefore covering energy needs. Secondly, by inhibiting glucagon secretion, it induces storage of glucose as glycogen in the liver and skeletal muscle to cover energy requirements in the absence of food consumption or during physical activity or exercise (Dimitriadis, et al., 2004).

Action

Insulin is an anabolic hormone, signaling the metabolism (utilization and storage) of carbohydrates, protein and fat in various tissues. Its function is to maintain a state of internal balance and physical well being in spite of changes in metabolic needs or outside internal or external factors (homeostasis). Since glucose is the major fuel for energy provision in cells, the regulation of its metabolism is of primary importance. The mechanism of action and

many of the effects of insulin are now well established (Dimitriadis, Mitrou, Lambadiari, Maratou, & Raptis, 2011).

Three tissues are important contributors to maintain homeostasis:

First, the liver is responsible for: (I) storing glucose as glycogen in the postprandial state and (II) providing the circulation with glucose through glycogenolysis and gluconeogenesis under conditions of fasting or increased energy demands, such as during exercise. Insulin inhibits glycogenolysis and gluconeogenesis, decreasing hepatic glucose production.

Second, skeletal muscle is primarily responsible for glucose uptake in the postprandial state. In muscle cells, glucose is metabolized through the glycolytic pathway and oxidized in the mitochondria to provide energy, or is stored as glycogen. Glycogenolysis in muscle cells is extremely important for the provision of energy during short bouts of high intensity exercise (sprinting, maximal strength resistance training etc.). In such cases, glycogen breakdown and anaerobic glucose metabolism increases the rate of lactate formation. Lactate is directed to the liver and is transformed back to glucose through gluconeogenesis (Cori cycle). As a result the rate of ATP formation is quickly increased to cover the increased energy demands. In muscle cells, insulin increases glucose uptake, glycogen synthesis, glycolysis and glucose oxidation.

In addition to glucose, insulin also regulates protein metabolism in skeletal muscle by increasing protein synthesis and decreasing protein degradation. As a result, insulin decreases the release of amino acids from muscle and increases their incorporation into muscle protein. Additionally, amino acid levels in the circulation are maintained within the normal range, fulfilling its role as an anabolic hormone.

Third, the adipose tissue is responsible for: (I) storing non-esterified fatty acids (NEFA) as triglycerides in the postprandial state and (II) degrading its stores through lipolysis to produce NEFA and cover energy needs of other tissues (mainly skeletal muscle) in the fasting state or during exercise, when glucose is scarce. In adipocytes, insulin increases lipid storage and decreases lipolysis (Newsholme & Dimitriadis 2001, Dimitriadis, Mitrou, Lambadiari,

Maratou & Raptis, 2011). An important action of insulin in adipose tissue is to upregulate blood flow through direct effects on the endothelial cells of arterioles and produce nitric oxide. The increase in blood flow in this tissue in the postprandial state is critical, since it helps to clear triglycerides and NEFAs from the circulation.

Glucose metabolism in the glycolytic pathway first induces its transport across the cell membrane. Glucose transport is an important step in cell metabolism as it controls the rate of glucose utilization. In muscle and fat cells, glucose transport is triggered by insulin, which translocates GLUT4 transporters from intracellular pools to the surface cell membrane. (Polonsky, Sturis, & Bell, 1996). The uptake of glucose in the liver cells is not sensitive to insulin and responds only to the concentrations of glucose. In muscle cells, in addition to the stimulation of glucose transport, insulin can directly stimulate: (I) hexokinase activity, thus increasing the rate of glucose phosphorylation, (II) glycogen synthase activity, thus increasing the rates of glycogen synthesis, (III) 6-phosphofructokinase activity, thus increasing the rates of glycolysis and (IV) pyruvate dehydrogenase activity, thus increasing glucose oxidation (Dimitriadis, Mitrou, Lambadiari, Maratou & Raptis, 2011).

II. Pathophysiology of Type 2 Diabetes

Hindered secretion is initiated at the prediabetic stage when, due to genetic predisposition, β-cells begin to decrease in mass and cell number. At this stage, when less than 50% of β-cells have been destroyed, plasma glucose levels are elevated only in the postprandial and not the fasting state. The percentage of β-cells which remain intact manage to keep fasting plasma glucose levels at desired standard and therefore measurements only in the fasting state fail to detect metabolic abnormalities. Meanwhile the postprandial hyperglycaemia has already started to cause tissue damage in a variety of tissues, including the vascular endothelium.

Once the β-cell mass and number is further decreased to under 50%, they fail to cope with the metabolic needs, resulting in elevated fasting plasma glucose levels over 126mg/dl. This fasting hyperglycaemia is due to the remaining β-cells' inability to secrete insulin even under

conditions of basal glycemia (Polonsky, Sturis, & Bell, 1996; Kahn, Hull, & Utzschneider, 2006; Μήτρου, Σιμιτζή & Δημητριάδης, 2016).

In order to understand why β-cell death occurs, one must trace the course of type 2 diabetes pathophysiology back to the prediabetic stage. As mentioned above, in this initial stage excessive hyperglycemia is apparent only in the postprandial and not the fasting state. On the other hand, diving into the physiology of adipose tissue, the causality effect of obesity comes into play.

A major role of adipose tissue is to store lipids in its cells, in the form of triglycerides. Excessive consumption of fat and carbohydrates affect both insulin sensitivity and release, coupled with overall over-nutrition causing obesity (Kahn, Hull, & Utzschneider, 2006). Obesity stems from an increase in the size of the adipocytes due to excessive caloric intake, forcing them to exceed their storing capacity. As caloric intake continues to increase, more and more triglycerides are being stored in adipocytes causing cellular metabolic stress. However, adipocyte increase is not accompanied by a respective increase in the number of intratissue blood vessels, required to preserve regular blood flow. As a result, cells begin to face ischaemia and undergo necrosis, which poses a localised threat within the tissue. This threat, as expected, recruits cells of the immune system (macrophages). The latter, secrete inflammatory cytokines (such as IL6, TNFa etc.), which produce a localised insulin resistance within the adipose tissue "protecting", to some degree, the adipocytes from further lipid storage (Dimitriadis, et al., 2004; Polonsky, Sturis, & Bell, 1996; Kahn, Hull, & Utzschneider, 2006; Μήτρου, Σιμιτζή & Δημητριάδης, 2016, Δημητριάδης, Μαράτου, Μουτσάτου, 2019).

If the excess in caloric intake is perpetuated, insulin resistance is increased further leading to an increase in lipolysis and production of NEFAs, which, along with inflammatory cytokines, escape the tissue into the bloodstream reaching other peripheral tissues.
The aforementioned hyperglycemia along with hyperlipidemia cause toxic damage to tissues, such as muscle, liver, adipose, as well as endothelial cells of blood vessel walls and β-cells (glucotoxicity, lipotoxicity) (Kahn, Hull, & Utzschneider, 2006; Μήτρου, Σιμιτζή & Δημητριάδης, 2016). This aggravates the genetically predisposed insulin resistance, forcing

the remaining β-cells to hypersecrete insulin leading to hyperinsulinemia (Philippou, Chryssanthopoulos, Maridaki, Dimitriadis & Koutsilieris, 2019; Polonsky, Sturis, & Bell, 1996). According to Polonsky et al. (1996), insulin resistance does not necessarily imply hyperglycemia, as long as glucose tolerance in intact and compensatory hyperinsulinemia is occuring. The "sensing" mechanism of the β-cells to secrete insulin depends on the metabolism of glucose in the glycolytic pathway (Polonsky, Sturis, & Bell, 1996). Therefore gluco- and lipotoxicity result in gradual apoptosis of β-cells through an increase in radical oxygen species (oxidative stress). Additionally, damaged β-cells fail to sense increases of blood glucose levels on time, leading to a significant delay of insulin secretion under conditions of hyperglycemia, such as after a meal.

Muscular tissue is genetically predisposed to suffer metabolically, as cell mitochondria are defective, hindering aerobic oxidation capacity. The infiltration of muscle tissue by NEFAs, aggregates an already unstable metabolic condition. Furthermore, NEFAs are also directed to the liver, stimulating gluconeogenesis and endogenous glucose production, also aggravating insulin resistance. Endothelial cells also face increased oxidative stress, which leads to a decrease in vascular compliance and blood flow in response to insulin. Moreover, oxidative stress induced by lipo- and glucotoxicity in endothelial cells, initiates the formation of atherosclerotic plaques in vessel wall and therefore cardiovascular disease. It is important to note that the formation of atherosclerotic plaques as a result of insulin resistance, precedes the clinical diagnosis of type 2 diabetes

In conclusion, insulin resistance is inherited and concerns all insulin-sensitive tissues. However, the gradual development of type 2 diabetes is initiated by an increase in adipose tissue mass, especially when accompanied by a sedentary lifestyle. Lipo- and glucotoxicity are the main mechanisms aggravating insulin resistance, ultimately leading to overt type 2 diabetes and cardiovascular disease (Dimitriadis, et al., 2004; Polonsky, Sturis, & Bell, 1996; Kahn, Hull, & Utzschneider, 2006; Μυγδάλης, 2016, Δημητριάδης, Μαράτου, Μουτσάτσου, 2019).

III. Importance of nutrition and exercise as a diabetes intervention

Successful management of T2D includes three fundamental principles; diet, exercise and medication, as portrayed in Figure 1. Obesity and sedentary lifestyle are the two main causes of the development of insulin resistance. Therefore an endeavour to achieve weight loss through diet, exercise and medication is the ultimate methodology for treating T2D (Franz, et al., 1994; Polonsky, Sturis, & Bell, 1996; Ozemek, Lavie, & Rognmo, 2019).

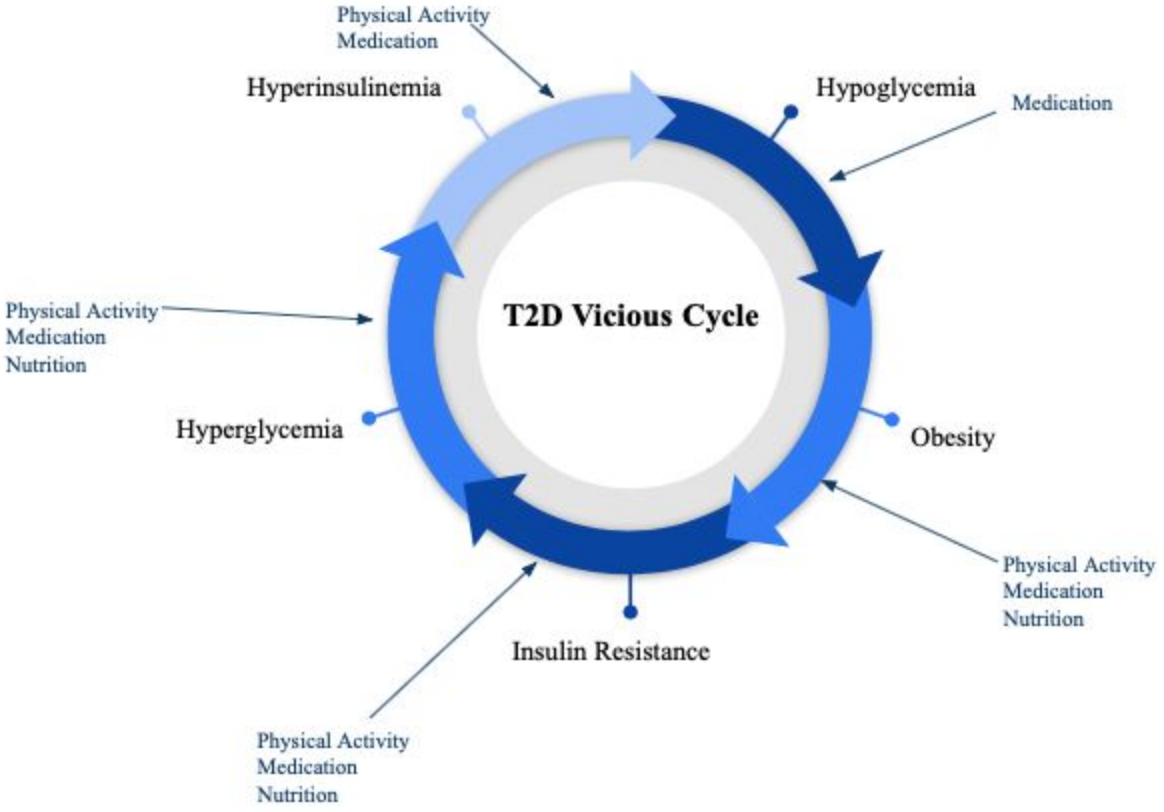

Figure 1. The vicious cycle of the pathophysiology of type 2 diabetes and the factors which each part of the intervention targets

Genetic predisposition results in defective insulin action and malfunctioning pancreatic and muscular cells. Defective cellular insulin response is essential but the epigenetically increased insulin resistance in hand with lipotoxicity due to obesity ultimately culminate to a diabetic phenotype. In order to break this malignant metabolic cycle one must trace the development of diabetes back to point zero, well before obesity and a sedentary lifestyle was adopted. When combating diabetes, medications alone will ultimately fail to reverse the

subject to point zero. Exercise interventions have been found to be superior in reducing visceral adipose tissue, which plays a pivotal role in the pathogenesis of the metabolic syndrome (Rao, et al., 2019).

Nutrition

Improved glycaemic control, improved insulin sensitivity, decreased glycosylated haemoglobin, insulin and blood lipid concentrations have been found following weight loss of as much as 5-10% of body weight (American Diabetes Association, 2002; Ash, et al., 2003). Nevertheless, the genetically predisposed role that the Central Nervous System plays in the modulation of body weight makes the sustainability of such weight loss interventions hard to achieve. In order to successfully maintain weight loss, a lifestyle change should be introduced, including exercise as a secondary pillar to diabetes management (American Diabetes Association, 2002; Ash, et al., 2003, Catenacci & Wyatt, 2007).

In general, caloric restriction by itself has been found to improve subject' glycemic profile, regardless of diet composition. However, intake of monounsaturated fat and carbohydrate instead of saturated fat has been found to decrease low-density lipoproteins to a greater extent (Heilbronn, Noakes, & Clifton, 1999). The American Diabetes Association (2002) recommends a decrease of saturated fat, cholesterol and sodium in order to combat high lipid and blood pressure levels. Finally, a high protein intake increases satiety, ultimately decreasing hunger and total caloric intake (Paddon-Jones, et al., 2008).

Exercise

Physical Activity has been found to be a key component for diabetes management, with both continuous as well as accumulated exercise being beneficial (Murphy, Lahart, Carlin, & Murtagh, 2019). It has been characterized as a diabetic "polypill" due to the numerous ways in which it alleviates the pathophysiology of the disease. More specifically, it ameliorates vascular compliance, therefore decreasing blood pressure, decreases oxidative and inflammatory stress, restores blood glucose and lipid stability. Pancreatic cell failure is also partially relieved (Teixeira-Lemos, Nunes, Teixeira, & Reis, 2011).

Insulin sensitivity is increased via exercise as intramuscular insulin-stimulated glycogen synthesis is doubled, stemming from higher insulin-stimulated glucose transport and phospohorylation (Perseghin, et al., 1996).

Physical Activity results in increased overall health, well being, glycemic control, insulin sensitivity, weight loss, while minimizing the risk of cardiovascular complications. It's therapeutic role stems in the improvement of subjects' glycemic control through insulin-independent mechanisms, therefore improving hyperglycaemia while reducing hyperinsulinemia. Muscle contractions increase muscle glucose uptake, while exercise in itself leads to improvement in glucose tolerance and Hb1Ac, through enhancing the translocation of GLUT 4 from the intracellular compartment to the cellular membrane of adipose and muscle cells, thus improving insulin sensitivity. Exercise is unique in the treatment of type 2 diabetes as, in contrast to medication, it can successfully minimize postprandial hyperglycemia without side effects (Ekelund, et al., 2019; (Philippou, et al., 2019; Δημητριάδης, Μαράτου, Μουτσάτσου, 2019).

It must be stated that a sedentary lifestyle could have had a causality effect on obesity in the first place via two main ways. First, the decrease of caloric expenditure due to lack of bodily movement and secondly the decreased basal metabolic expenditure due to decreased muscle mass. Therefore its rational that exercise protocols should include both aerobic exercise to increase total caloric expenditure as well as resistance training to induce muscular hypertrophy, therefore increased basal caloric expenditure (Strasser, 2012). More specifically, both aerobic and strength training decrease Hb1Ac levels, with strength training also improves skeletal muscle insulin sensitivity. Enhanced glycemic control is a primary result of strength training as muscle accounts for 85% of glucose uptake. As a result, the guidelines for physical activity in T2D patients include a combination of both aerobic and strength training for a total of over 150 minutes per week. (Philippou, et al., 2019)

Aerobic Exercise acts on both sides of insulin related pathophysiology. More specifically it primarily combats insulin resistance in insulin-dependent cells by insulin transporters proliferation. Secondarily, it breaks the pathophysiologic cycle of diabetes by decreasing adipokines, as well as inflammatory and oxidative stress. Finally insulin signaling is enhanced as adipokines, oxidative stress, ceramide levels are decreased, GLUT 4 receptors,

beta cell function and capillary density are increased (Yaribeygi, Atkin, Simental-Mendía, & Sahebkar, 2019).

III. Purpose

The purpose of this case study was to apply a multidimensional lifestyle intervention specifically tailored to the needs of a diabetic patient and quantify the extent to which such an intervention can potentially make a real difference in the life of such a patient, who represents the majority of similar cases seen in the outpatient units.

METHODOLOGY

I. Demographics

Table I. Subject Demographics including: age, height, bodyweight, medical diagnoses and medication

Age	65
Height	187cm
Pre-intervention weight	131kg
Medical Diagnoses	Coronary heart disease & Triple bypass surgery (2004) (Appendix A) Cardiovascular disease Type 2 Diabetes (2004) Myeloproliferative syndrome (2012) (Appendix B) Sleep Apnea (2016) (Appendix C) Retinopathy (2019)
Pre-intervention Medication	Liraglutide (Victoza) 6mg/ml Insulin degludec (Tresiba) 100U/ml Atorvastatin (Antorcin) 20mg Fluoxetine (Fokeston) 20mg Acetylsalicylic acid (Salospir) 100mg Hydroxycarbamide (Hydroxyurea) 500mg Insulin Aspart (Novorapid FlexPen) 100 mon/ml
Post-intervention Medication	↑Liraglutide (Victoza) 6mg/ml ↑Insulin degludec (Tresiba) 100U/ml Atorvastatin (Antorcin) 20mg Fluoxetine (Fokeston) 20mg Acetylsalicylic acid (Salospir) 100mg Hydroxycarbamide (Hydroxyurea) 500mg →Metformin (Glucophage) 1000mg

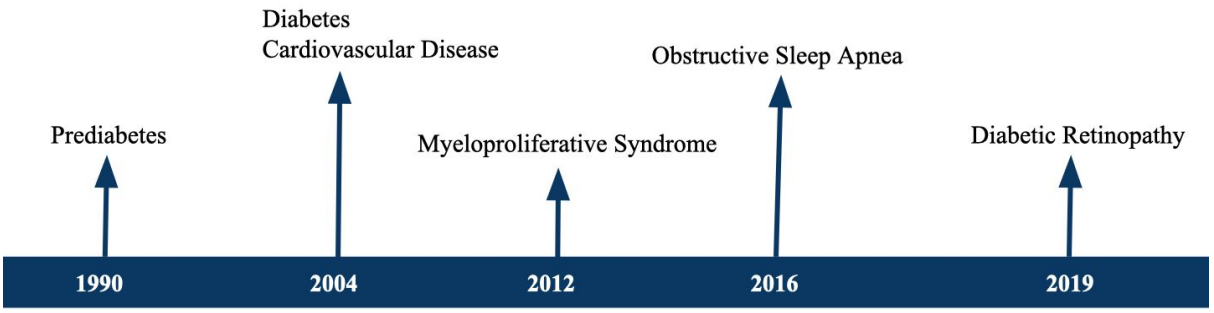

Figure 1. Timeline of the subject's medical diagnoses from 1990 to 2019.

II. Intervention

For the purposes of this study a 65 year old male with type 2 diabetes underwent a lifestyle intervention, including modifications of medications, nutritional habits and physical activity levels.

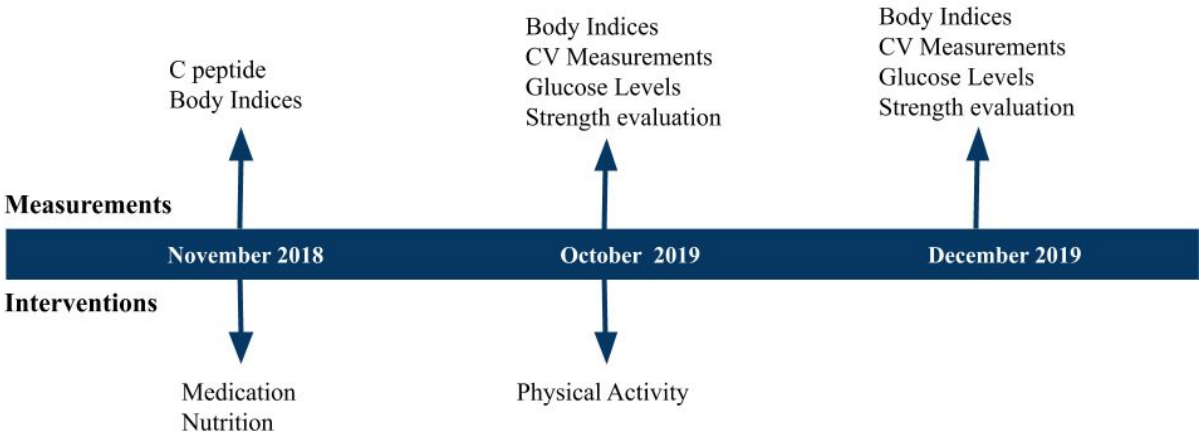

Figure 2. Timeline of the intervention and measurements taken from November 2018 to December 2019.

Medication

An individualized pharmaceutical intervention including the increase of GLP1, long-lasting basal insulin, discontinuation of fast acting insulin and the prescription of Metformin (Glucophage). These changes were done as a result of the C peptide test the subject underwent in 2018 (Appendix D), which depicted that the number of functioning β-cells were unable to cope with postprandial insulin secretion demands, but could cope with fasting demands. This was done to eradicate his constant hypoglycaemic state, in an endeavour to decrease his appetite and therefore his constant weight gain.

Nutrition

His nutritional habits were altered in a way to decrease high carbohydrate and fat intake and increase protein intake. Foods with high glycemic index were substituted by low glycemic index equivalents to decrease glucose spikes. Protein intake was increased as it has been found to ultimately decrease food intake and increase satiety (Jakubowicz & Froy, 2013; Paddon-Jones, et al., 2008).

Physical Activity

Physical activity patterns were also utterly changed as the subject went from a sedentary lifestyle to an active daily plan, were he was encouraged to walk as much as possible during the day and also work out every day. His fitness training plan was based on the Greek Central Board of Health (2018) and ACSM Guidelines for Physical Activity in subjects with type 2 diabetes and cardiovascular disease. It included strength training in a gym every other day, for a total of three days per week and walking on rest days for a total of four days a week. More specifically, as the guidelines state, strength training was done on nonconsecutive days, working at 50-80% of the subject's 1-RM, between 8-15 repetitions, starting with more and decreasing them as the subject's strength increased. Aerobic training was also performed at 40-60% of his VO2max. This intensity was achieved through monitoring his heart rate, where 70% of HRmax was aimed for. Aerobic training sessions were less structured than strength training ones, including walks in nature etc, as this was of the subjects liking and decreased his chance of withdrawal from the intervention (Colberg, 2017**)** .

Measurements

Measurements included bodyweight, waist and hip circumference, fluctuations of glucose levels, heart rate during workouts, psychological state. Bodyweight was measured using a Fitbit Aria scale, as it was connected to his phone app, increasing therefore his interest in improving and sticking with the intervention. Waist circumference was measured with tape, at "midpoint between the lower margin of the last palpable rib and the top of the iliac crest" and the hip circumference at the widest portion, as suggested by the World Health Organization (2011). This measurement was included to estimate visceral adipose tissue, which as aforementioned plays a critical role in insulin resistance. Interstitial fluid glucose levels were monitored about six times a day, including pre and post breakfast, lunch and dinner measurements (Freestyle Libre was scanned six times per day). A Freestyle Libre patch was used in order to ensure data accuracy, as any changes in plasma glucose levels are identified by the patch within five minutes. Moreover, it enables us to monitor changes in plasma glucose values continuously (Petrie et al., 2018; Rodbard, 2016). Postprandial glucose values were not taken at a set time period following meal consumption, but rather at the peak from baseline levels, which varies depending on the meal consumed. Workout heart rate monitoring was done pre and post intervention, in order to identify and heart adaptations to training. For psychological monitoring, the Center for Epidemiologic Studies Depression Scale (CES-D) was used (Friis & Nanjundappa, 1986). It was filled out at the beginning and the end of the intervention in order to delineate any changes in his depressive psychological state.

RESULTS

I. Glucose Levels

Fluctuations of glucose levels were monitored continuously, using a Freestyle Libre patch, which can be viewed in Figure 2 for the Pre-intervention and Figure 3 for the Post-intervention period. Glucose levels were found to be within the target range (between 100-140mg/dL) for pre-intervention 8% and 32% for post-intervention. The pre-intervention period when the primary measurements were recorded, was from October 4th to 18th. The intervention period measurements were from December 2nd to 22nd. There was a 1.1% decrease in HbA1C levels (glycated hemoglobin), from 7.5% (58 mmol/mol) pre-intervention to 6.4% (46 mmol/mol) post-intervention. The average fluctuations of glucose levels in interstitial fluid as measured by Freestyle were as follows. Fasting glucose levels, as measured in the morning, decreased by ~25% , from 149 to 113mg/dL. Postprandial glucose levels also decreased, for breakfast by ~27%, from 192 to 141mg/dL, for lunch by ~18%, from 172 to 141 mg/dL, for dinner by ~31%, from 185 to 128mg/dL.

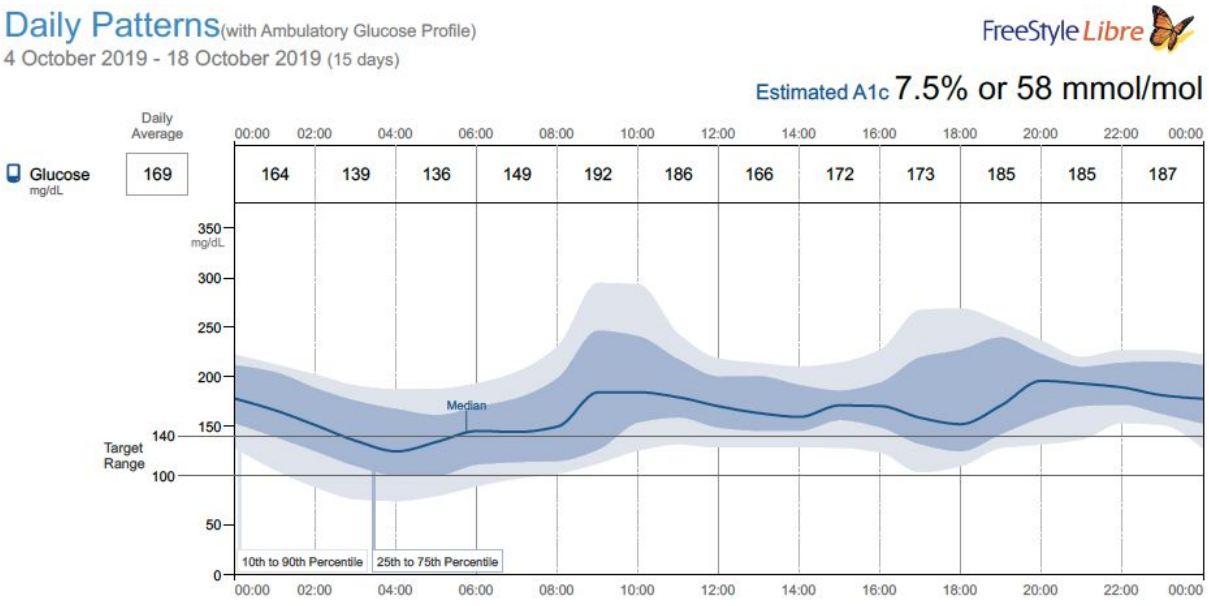

Figure 2. Interstitial fluid glucose level fluctuations as monitored continuously by a Freestyle Libre patch during the Pre-intervention period October 4th to October 18th.

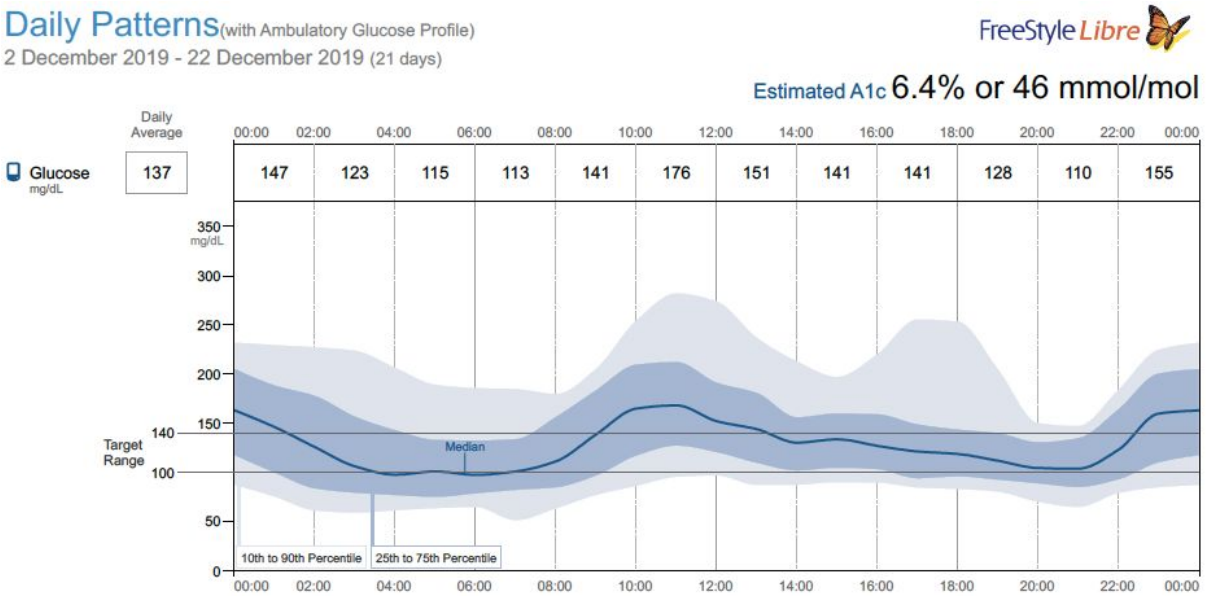

Figure 3. Interstitial fluid glucose level fluctuations as monitored continuously by a Freestyle Libre patch during the Post-intervention period December 2nd to December 22nd.

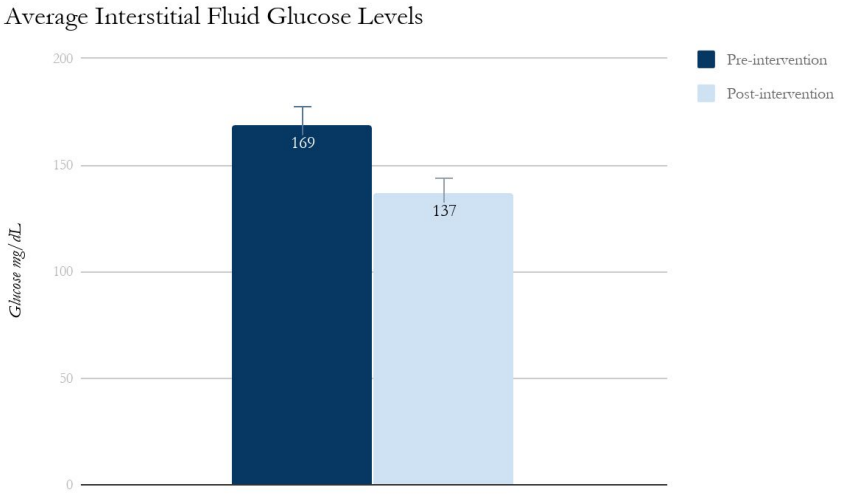

Figure 4. Average glucose levels in the interstitial fluid for pre-intervention (October 4th to 18th) and post-intervention (December 2nd to 22nd) periods.

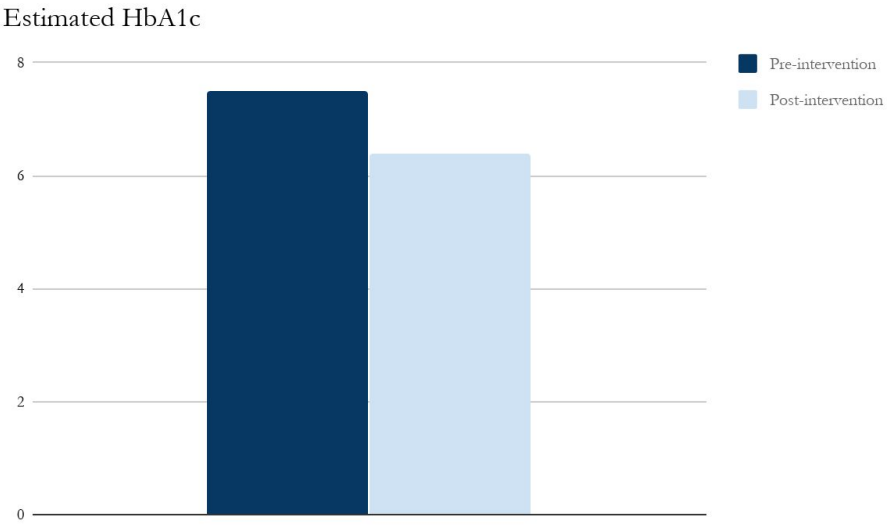

Figure 5. Estimated HbA1c (glycated hemoglobin) levels for pre-intervention (October 4th to 18th) and post-intervention (December 2nd to 22nd) periods.

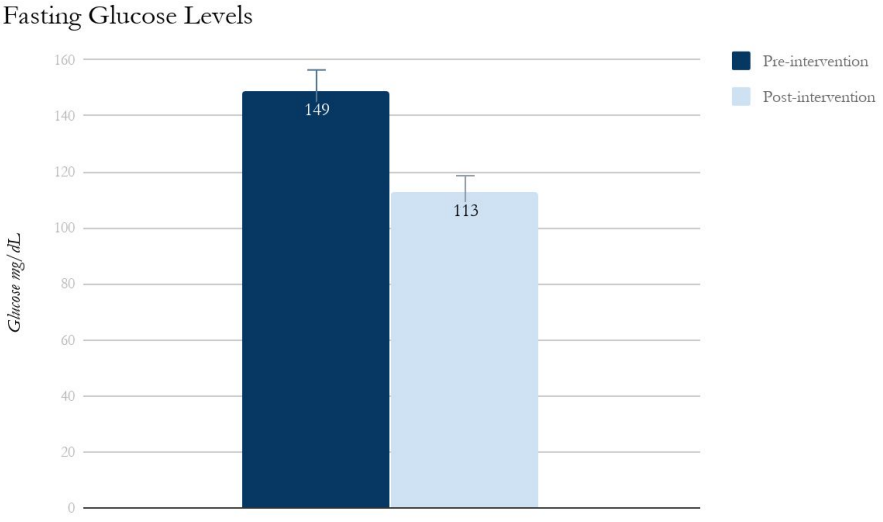

Figure 6. Average fasting glucose levels in the interstitial tissue for pre-intervention (October 4th to 18th) and post-intervention (December 2nd to 22nd) periods.

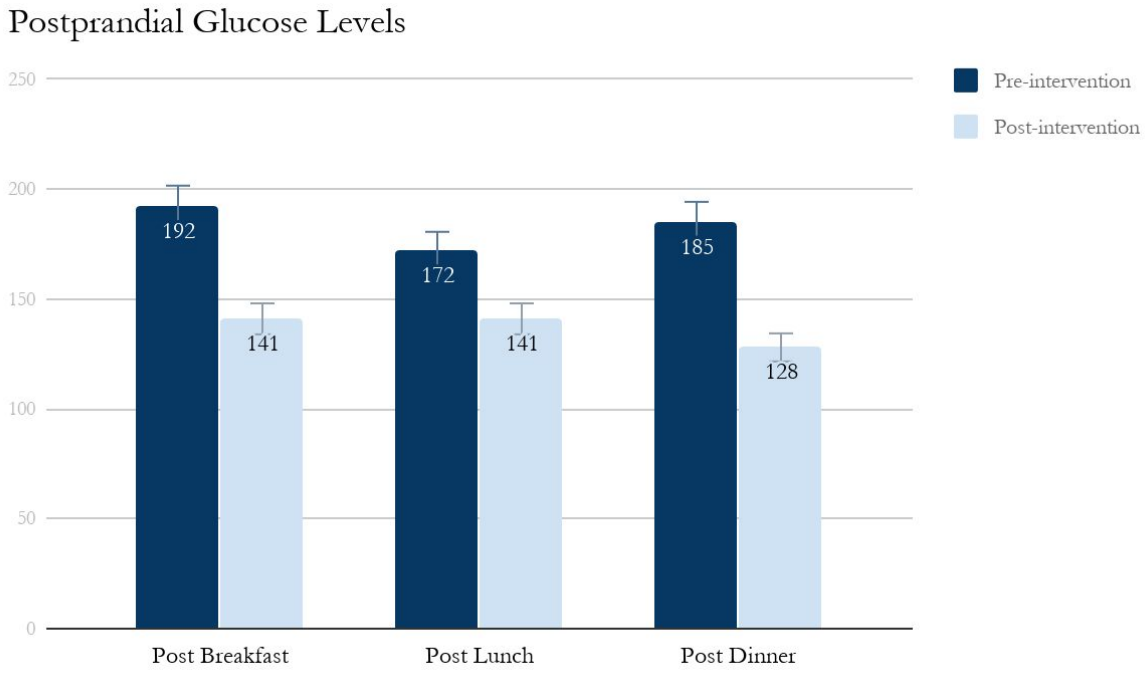

Figure 7. Average postprandial glucose levels in the interstitial tissue for pre-intervention (October 4th to 18th) and post-intervention (December 2nd to 22nd) periods.

II. Body Indices

The subject's weight decreased by approximately 10%, from 136 to 125, accompanied by an 8% decrease in waist circumference, from 141cm to 130 cm. The Waist to Hip Ratio decreased from 1.184 to 1.092.

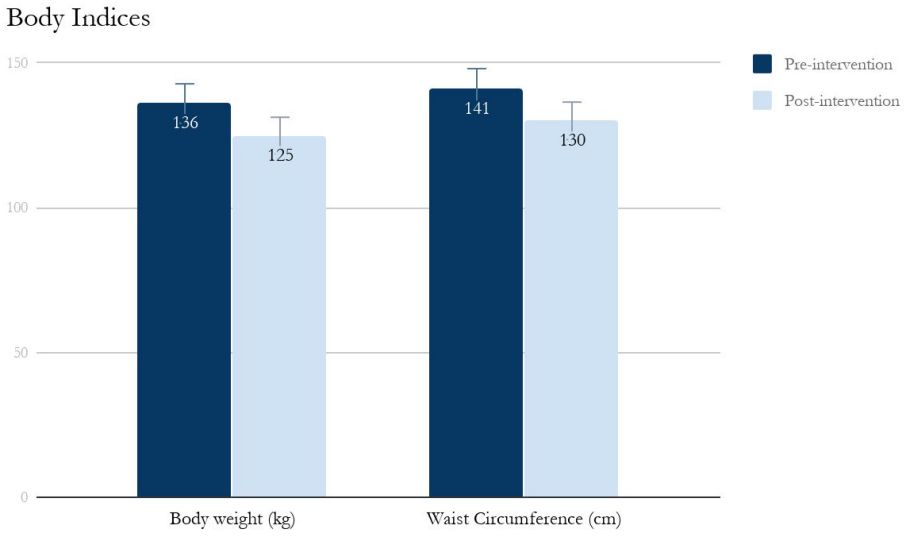

Figure 8. Body weight and respective waist circumference measurements for pre- (March, 2018) and post-intervention (Dec, 2019)

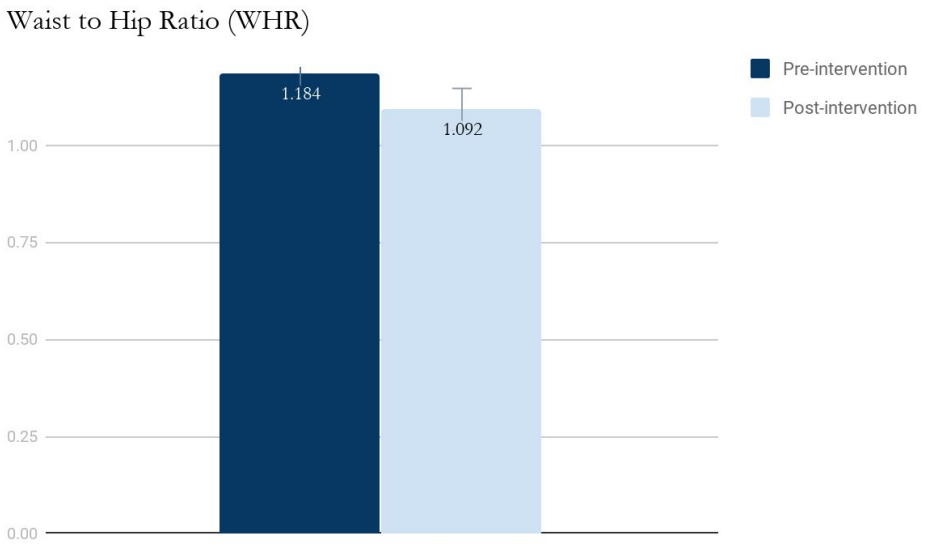

Figure 9. Waist to Hip Ratio (WHR) for pre- (January, 2018) and post-intervention (Dec, 2019)

III. Strength

Changes in strength are depicted in Figure 10 as measured by the baseline pre-intervention training session and the post-intervention training session. Six main exercises were used to portray the strength changes in three main muscle groups, upper back, chest and legs. In average strength increased by 54%. Although the training sessions were altered as the subject progressed, and repetitions were decreased, as the guidelines suggest, the values provided in the figure are all for the same number of repetitions.

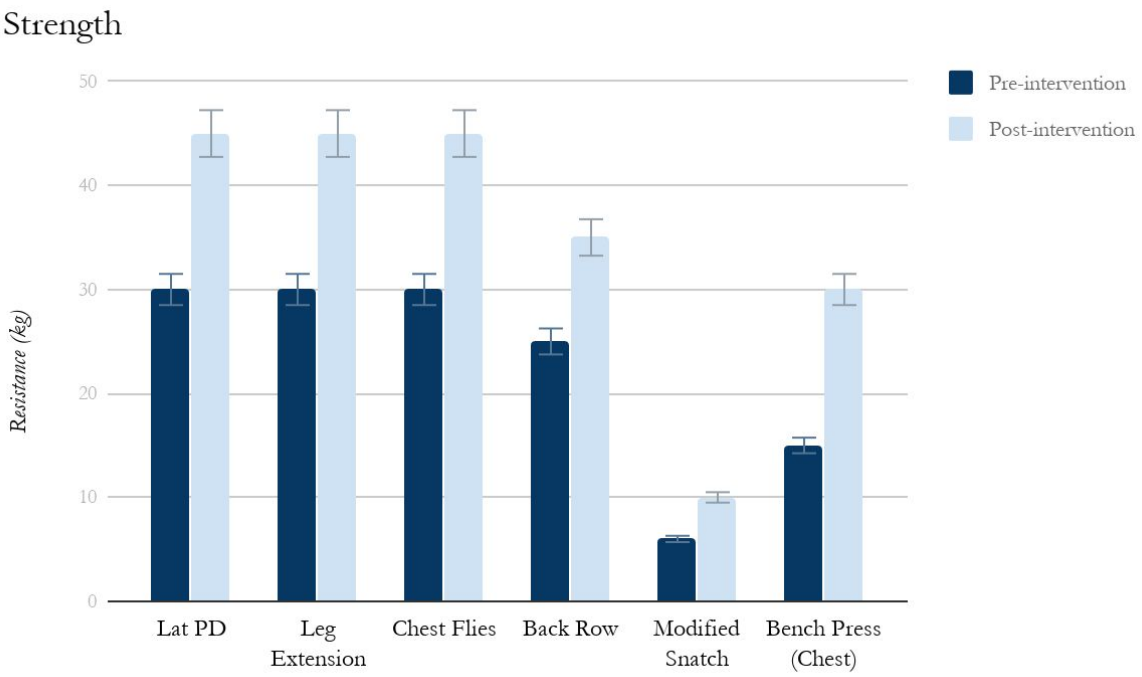

Figure 10. Muscle strength as measured through resistance (kg) used in resistance training sessions

IV. Heart Rate

Heart rate measurements were done during his first resistance training session, for a total of 18 sets (6 exercises for 3 sets each), in a session that lasted ~20 minutes. Then at the end of the intervention, the same workout routine, with identical repetitions and weight was repeated and heart rate measurements were taken again. The results measured by the chest heart rate monitor are displayed in figure 11. Both maximal and average heart rate values decreased. Maximal by 15%, from 118 to 101 beats per minute and average by 12%, from 142 to 126 beats per minute.

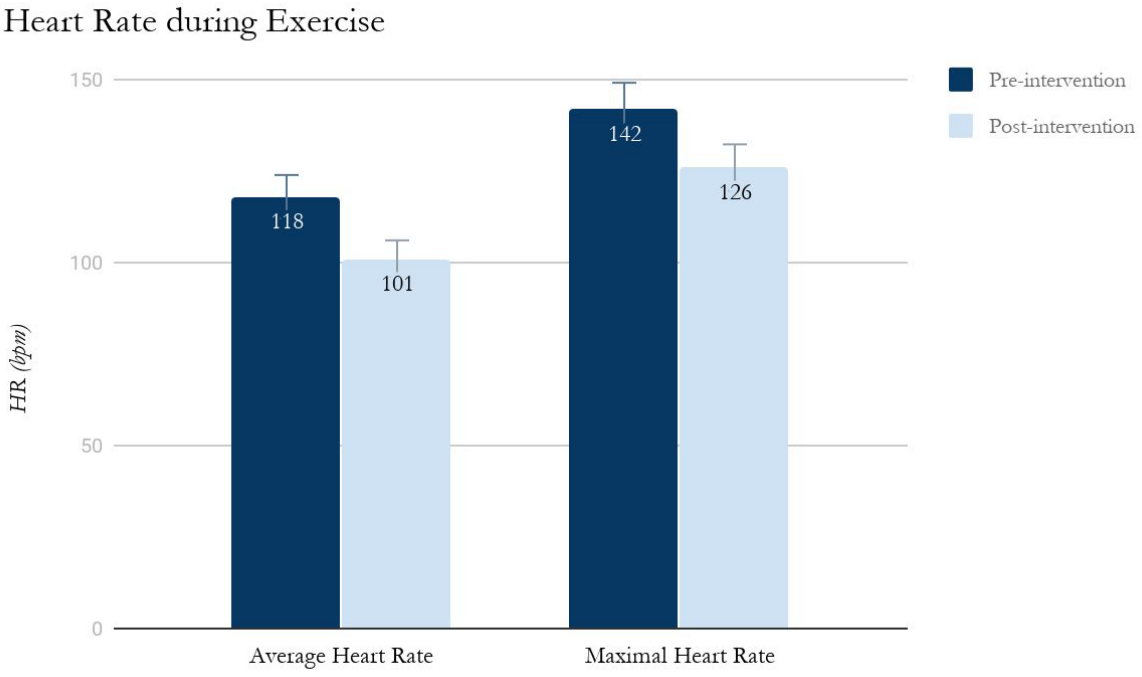

Figure 11. Average and Maximal heart rate in beats per minute, as measured during the baseline pre-intervention and post-intervention identical training sessions.

V. Psychological State

The subject's psychological state, and more specifically the occurrence of depressive -- was radically decreased through the intervention. The subject reported an increase in the CES-D Score by over 80%.

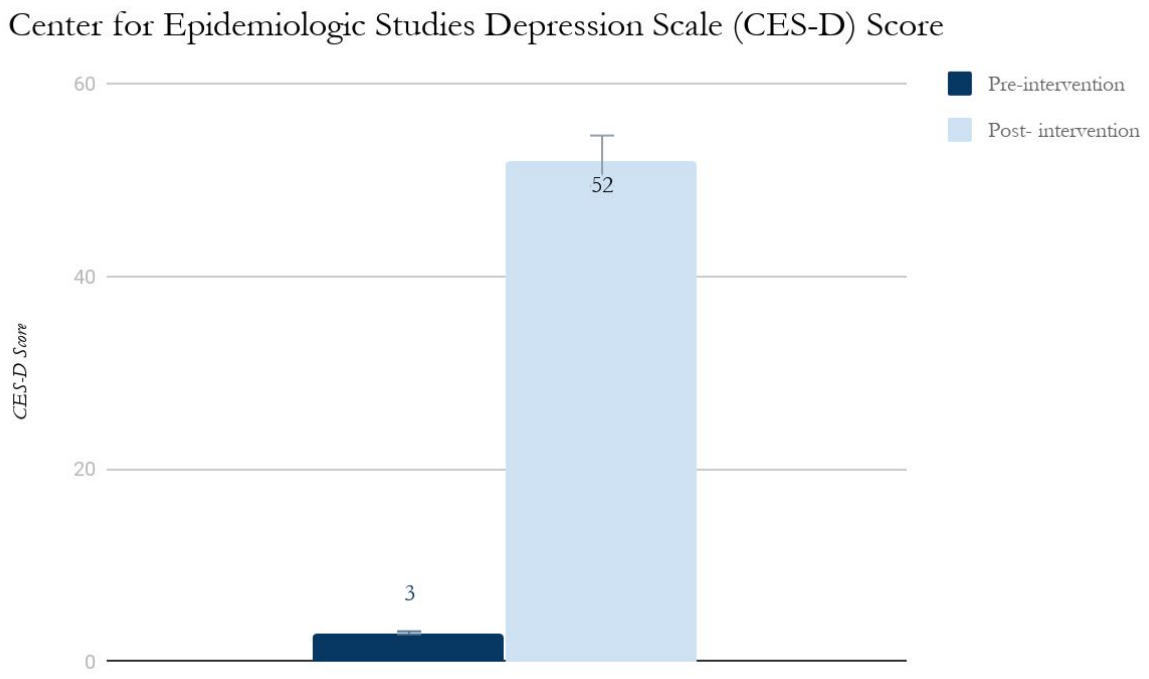

Figure 12. Center for Epidemiologic Studies Depression Scale (CES-D) score, as measured pre- (March 2018) and post-intervention (December 2019).

DISCUSSION

I. Glucose Levels

All interstitial fluid glucose values, including average, fasting and postprandial decreased, as expected. This depicts an improvement in insulin sensitivity, which could be due to an increase in muscle mass via resistance training and an improvement in the aerobic metabolism of glucose via aerobic training. Moreover, this could also be a result of the changes in nutritional patterns, as carbohydrate and fat intake were reduced, thus decreasing glucose fluctuations. Finally, another factor improving glucose levels could be the radical weight loss which, as Ash et al. (2003) have concluded, can improve fasting and average hyperglycemia.

II. Body Indices

The subject's body weight decreased by approximately 10%, making it a substantial change which could have metabolic impacts. Waist circumference also decreased to a great extent. It must be stated that the subject has mainly visceral adipose tissue, which is why the body weight loss in kilograms matches closely the decrease in waist circumference, alluding to the fact that the majority of adipose tissue loss was visceral. This is important since, for mechanistic reasons, visceral adiposity is a major factor responsible for the development of insulin resistance in obesity and type 2 diabetes.

Strength was found to increase by approximately 50%, indicating muscular hypertrophy. An increase in muscle mass could greatly impact glucose uptake, therefore increasing insulin sensitivity. Moreover, higher muscle mass increases one's basal metabolic rate, therefore sustaining weight loss.

III. Heart Rate

Average and maximal HR both decreased depicting a decreased cardiovascular stress induced by the identical resistance training session. This could be due to the fact that muscular contractions lead to insulin-independent glucose uptake, therefore decreasing the need for high blood flow to the active musculature and as a result lower cardiac stress (Philippou, et al., 2019).

IV. Psychological State

One should be cautious when evaluating the results obtained via the CES-D, as the score is self- reported and therefore could be susceptible to self-biases. Nonetheless, the subject reported a radically increased improvement in feelings of well-being, which has been reported to be an exercise-induced outcome for subjects with diabetes due to the reduction of the chronic stress (Dimitriadis, Mitrou, Lambadiari, Maratou, & Raptis, 2011; Philippou, et al., 2019).

CONCLUSION

Lifestyle changes, subject-tailored medications, nutrition and physical activity resulted in an increase in insulin sensitivity, metabolism improvement, and a decrease in cellular metabolic and cardiovascular stress. Significant changes were found in all measurements taken, delineating an immeasurable health and quality of life improvement. Exercise is indeed a pleiotropic "polypill" as characterized by Teixeira-Lemos, et al., contributing to a great improvement in the subjects metabolic profile (2011). Nevertheless, we must keep in mind that the subject has been suffering from overt diabetes for over fifteen years with poor glycemic control, making it extremely difficult to return back to the prediabetic stage, due to extensive tissue damage.

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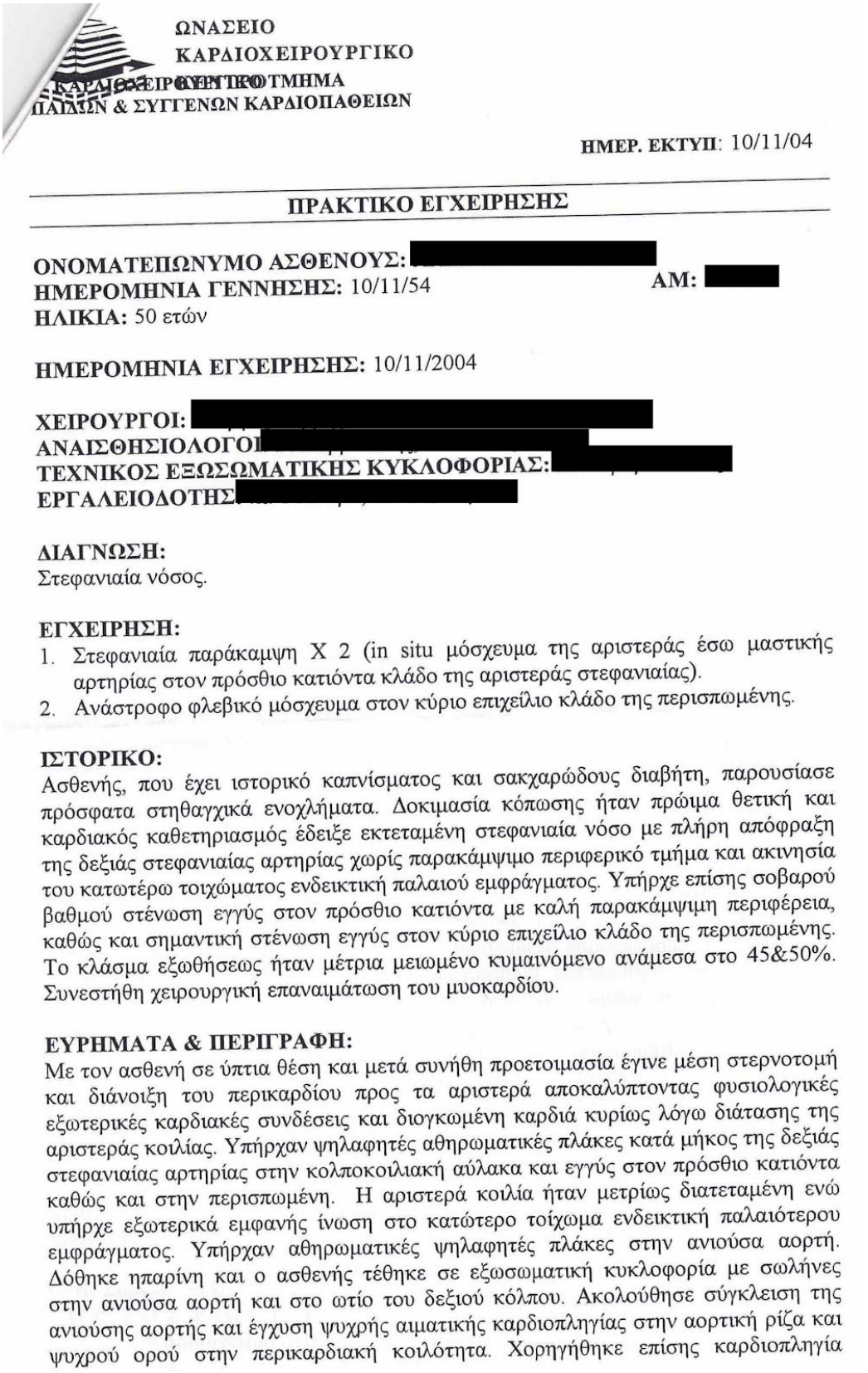
Appendix A



ΩΝΑΣΕΙΟ
ΚΑΡΔΙΟΧΕΙΡΟΥΡΓΙΚΟ
ΚΑΡΔΙΟΧΕΙΡΟΥΡΓΙΚΟ ΤΜΗΜΑ
ΠΑΙΔΩΝ & ΣΥΓΓΕΝΩΝ ΚΑΡΔΙΟΠΑΘΕΙΩΝ

ΗΜΕΡ. ΕΚΤΥΠ: 10/11/04

ΠΡΑΚΤΙΚΟ ΕΓΧΕΙΡΗΣΗΣ

ΟΝΟΜΑΤΕΠΩΝΥΜΟ ΑΣΘΕΝΟΥΣ: [redacted]
ΗΜΕΡΟΜΗΝΙΑ ΓΕΝΝΗΣΗΣ: 10/11/54 **ΑΜ:** [redacted]
ΗΛΙΚΙΑ: 50 ετών

ΗΜΕΡΟΜΗΝΙΑ ΕΓΧΕΙΡΗΣΗΣ: 10/11/2004

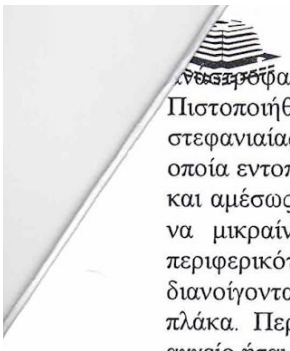
ΧΕΙΡΟΥΡΓΟΙ: [redacted]
ΑΝΑΙΣΘΗΣΙΟΛΟΓΟΙ [redacted]
ΤΕΧΝΙΚΟΣ ΕΞΩΣΩΜΑΤΙΚΗΣ ΚΥΚΛΟΦΟΡΙΑΣ: [redacted]
ΕΡΓΑΛΕΙΟΔΟΤΗΣ [redacted]

ΔΙΑΓΝΩΣΗ:
Στεφανιαία νόσος.

ΕΓΧΕΙΡΗΣΗ:
1. Στεφανιαία παράκαμψη Χ 2 (in situ μόσχευμα της αριστεράς έσω μαστικής αρτηρίας στον πρόσθιο κατιόντα κλάδο της αριστεράς στεφανιαίας).
2. Ανάστροφο φλεβικό μόσχευμα στον κύριο επιχείλιο κλάδο της περισπωμένης.

ΙΣΤΟΡΙΚΟ:
Ασθενής, που έχει ιστορικό καπνίσματος και σακχαρώδους διαβήτη, παρουσίασε πρόσφατα στηθαγχικά ενοχλήματα. Δοκιμασία κόπωσης ήταν πρώιμα θετική και καρδιακός καθετηριασμός έδειξε εκτεταμένη στεφανιαία νόσο με πλήρη απόφραξη της δεξιάς στεφανιαίας αρτηρίας χωρίς παρακάμψιμο περιφερικό τμήμα και ακινησία του κατωτέρω τοιχώματος ενδεικτική παλαιού εμφράγματος. Υπήρχε επίσης σοβαρού βαθμού στένωση εγγύς στον πρόσθιο κατιόντα με καλή παρακάμψιμη περιφέρεια, καθώς και σημαντική στένωση εγγύς στον κύριο επιχείλιο κλάδο της περισπωμένης. Το κλάσμα εξωθήσεως ήταν μέτρια μειωμένο κυμαινόμενο ανάμεσα στο 45&50%. Συνεστήθη χειρουργική επαναιμάτωση του μυοκαρδίου.

ΕΥΡΗΜΑΤΑ & ΠΕΡΙΓΡΑΦΗ:
Με τον ασθενή σε ύπτια θέση και μετά συνήθη προετοιμασία έγινε μέση στερνοτομή και διάνοιξη του περικαρδίου προς τα αριστερά αποκαλύπτοντας φυσιολογικές εξωτερικές καρδιακές συνδέσεις και διογκωμένη καρδιά κυρίως λόγω διάτασης της αριστεράς κοιλίας. Υπήρχαν ψηλαφητές αθηρωματικές πλάκες κατά μήκος της δεξιάς στεφανιαίας αρτηρίας στην κολποκοιλιακή αύλακα και εγγύς στον πρόσθιο κατιόντα καθώς και στην περισπωμένη. Η αριστερά κοιλία ήταν μετρίως διατεταμένη ενώ υπήρχε εξωτερικά εμφανής ίνωση στο κατώτερο τοίχωμα ενδεικτική παλαιότερου εμφράγματος. Υπήρχαν αθηρωματικές ψηλαφητές πλάκες στην ανιούσα αορτή. Δόθηκε ηπαρίνη και ο ασθενής τέθηκε σε εξωσωματική κυκλοφορία με σωλήνες στην ανιούσα αορτή και στο ωτίο του δεξιού κόλπου. Ακολούθησε σύγκλειση της ανιούσης αορτής και έγχυση ψυχρής αιματικής καρδιοπληγίας στην αορτική ρίζα και ψυχρού ορού στην περικαρδιακή κοιλότητα. Χορηγήθηκε επίσης καρδιοπληγία



ανάστροφα στον στεφανιαίο κόλπο. Επετεύχθη αμέσως διαστολική καρδιακή παύση. Πιστοποιήθηκε ότι δεν υπήρχαν παρακάμψιμοι περιφερικοί κλάδοι της δεξιάς στεφανιαίας αρτηρίας. Εξετάστηκε η πλάγια επιφάνεια της αριστεράς κοιλίας στην οποία εντοπίστηκε ο κύριος επιχείλιος κλάδος της περισπωμένης. Στην μεσότητά του και αμέσως πριν τον διχασμό υπήρχε αθηρωματική πλάκα, με το αγγείο περιφερικά να μικραίνει σημαντικά σε διάμετρο. Έγινε κατάλληλη αρτηριοτομή αμέσως περιφερικότερα της πλάκας αυτής. Η αρτηριοτομή επεξετάθη κεντρικότερα διανοίγοντας (και επομένως καταργώντας αιμοδυναμικά) την αθηρωματική αυτή πλάκα. Περιφερικά ήταν εφικτή η τοποθέτηση probe 1mm ενώ κεντρικότερα το αγγείο ήταν σαφώς μεγαλύτερης διαμέτρου. Στην αρτηριοτομή αυτή που ήταν αρκετά επιμήκης έγινε η περιφερική αναστόμωση ανάστροφου φλεβικού μοσχεύματος τελικοπλάγια με συνεχή ραφή 7-0 prolene. Χορήγηση καρδιοπληγίας μέσω του μοσχεύματος πιστοποίησε την άριστη ροή αυτού και την αιμοστατικότητα της αναστόμωσης. Μετά πρόσθετη χορήγηση καρδιοπληγίας και στην αορτική ρίζα ορθόδρομα και ανάστροφα στον στεφανιαίο κόλπο, επελέγη κατάλληλο σημείο αριστερά της ανιούσης αορτής. Στο σημείο αυτό δημιουργήθηκε panch aortotomy και σ' αυτό έγινε η κεντρική αναστόμωση του φλεβικού μοσχεύματος τελικοπλάγια με συνεχή ραφή 6-0 prolene. Μετά πρόσθετη χορήγηση καρδιοπληγίας εντοπίστηκε ο πρόσθιος κατιόντας στην μεσότητά του και στο σημείο αυτό έγινε κατάλληλη αρτηριοτομή εισερχόμενοι σε αυλό διαμέτρο 1,75mm. Η αρτηριοτομή έγινε μέσω περιφερικότερα της αποφρακτικής βλάβης. Περιφερικά στον πρόσθιο κατιόντα υπήρχαν μικρές αθηρωματικές πλάκες χωρίς όμως καμιά ένδειξη στένωσης. Στην αρτηριοτομή του προσθίου κατιόντα έγινε η περιφερική αναστόμωση της αρχικά παρασκευασθείσης in situ αριστεράς έσω μαστικής αρτηρίας τελικοπλάγια με συνεχή ραφή 8-0 prolene. Απελευθερώνοντας προσωρινά την ροή στο μόσχευμα της μαστικής πιστοποιήθηκε άριστη ροή αυτής μέσω της άμεσης πλήρωσης του περιφερικού τμήματος του προσθίου κατιόντα και των διαγωνίων κλάδων του και της ταχείας αύξησης της μυοκαρδιακής θερμοκρασίας στην κορυφή. Ο μίσχος της in situ έσω μαστικής στηρίχθηκε στο επικάρδιο της αριστεράς κοιλίας με 7-0 prolene. Αρχισε επαναθέρμανση του ασθενούς και μετά την προσεκτική εξαέρωση της ανιούσης αορτής, αφαιρέθηκε η αορτολαβίδα. Σύντομα αποκαταστάθηκε φλεβοκομβικός ρυθμός. Τοποθετήθηκαν ηλεκτρόδια προσωρινής βηματοδότησης και μετά την πλήρη επαναθέρμανση του ασθενούς έγινε εύκολα η διακοπή της εξωσωματικής κυκλοφορίας με άριστες αιμοδυναμικές παραμέτρους. Το ΗΚΓ ήταν φυσιολογικό. Διοισοφάγειο υπερηχοκαρδιογράφημα πιστοποίησε την πολύ καλή λειτουργία της αριστεράς κοιλίας η οποία ήταν βελτιωμένη σε σχέση με την προεγχειρητικά διαπιστωθείσα λειτουργία, περιλαμβανομένης και της κινητικότητας του κατωτέρου τοιχώματος της αριστεράς κοιλίας. Ακολούθησε αφαίρεση των σωλήνων εξωσωματικής, χορήγηση πρωταμίνης, προσεκτική αιμόσταση, συνήθης σύγκλειση των τραυμάτων (1ον της σαφηνεκτομής από τον αριστερό μηρό και 2ον της στερνοτομής, μετά τοποθέτηση σωλήνα παροχέτευσης) και μεταφορά του ασθενούς στην μονάδα εντατικής θεραπείας σε άριστη αιμοδυναμική κατάσταση.

Χρόνος κλειστής αορτής: 135'
Χρόνος εξωσωματικής κυκλοφορίας: 162'

Appendix B

Περιφερειακό Πανεπιστημιακό Γενικό Νοσοκομείο Θεσσαλίας
Εργαστήριο Παθολογικής Ανατομικής
Διευθυντής Γεώργιος Κ. Κουκούλης

ΕΚΘΕΣΗ ΙΣΤΟΠΑΘΟΛΟΓΙΚΗΣ ΕΞΕΤΑΣΗΣ

ΑΡΙΘΜΟΣ ΠΡΩΤΟΚΟΛΛΟΥ
4482/12

Ονοματεπώνυμο: [redacted]
Φύλο: άρρεν
Ηλικία: 56 ετών

Ημερομηνία παραλαβής: 11/5/12
Παραπέμπων ιατρός: κ. Κυριάκου
Κλινική: **Αιμοδοσία**
Κλινικές πληροφορίες:
Ανατομικό παρασκεύασμα: Οστεομυελική βιοψία

ΑΞΙΟΛΟΓΗΣΗ ΙΣΤΟΠΑΘΟΛΟΓΙΚΩΝ ΕΥΡΗΜΑΤΩΝ

Ιστολογικά παρατηρείται αυξημένη κυτταροβρίθεια του μυελού (τα λιποκύτταρα καταλαμβάνουν το 30% της εκτάσεως των μυελοχώρων). Παρατηρείται υπερπλασία της κοκκιώδους και της μεγακαρυοκυτταρικής σειράς. Η τελευταία εκπροσωπείται από ευμεγέθη κύτταρα με πολυλοβωτούς υπερχρωματικούς πυρήνες και τάση άθροισης σε ομάδες. Η ερυθρά σειρά εκπροσωπείται με ήπια δυσερυθροποιία. Στο υπόστρωμα ανιχνεύεται εστιακή αύξηση δικτυωτών ινών (Reticulin grade I).
Η εικόνα είναι συμβατή με μυελοϋπερπλαστικό σύνδρομο. Μορφολογικά αυξημένος αριθμός βλαστών δεν τεκμηριώνεται. Εν τούτοις δεν είναι διαθέσιμο αυτή τη στιγμή στο εργαστήριο CD34 για ανοσοϊστοχημική μελέτη.
Συνιστάται προσεκτική κλινικοεργαστηριακή διερεύνηση του ασθενούς (κυτταρογενετική μελέτη, επιχρίματα μυελού, περιφερικού αίματος κλπ.) και παρακολούθηση του ασθενούς.

ΜΑΚΡΟΣΚΟΠΙΚΗ ΠΕΡΙΓΡΑΦΗ

Ένας ιστικός κύλινδρος μήκους 1εκ.

ΙΑΤΡΟΣ

Appendix C

ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΘΕΣΣΑΛΙΑΣ
ΕΡΓΑΣΤΗΡΙΟ ΜΕΛΕΤΗΣ ΔΙΑΤΑΡΑΧΩΝ ΤΗΣ ΑΝΑΠΝΟΗΣ ΣΤΟΝ ΥΠΝΟ

Λάρισα, 15/12/2016

Ονοματεπώνυμο: [redacted]
Ηλικία: 62
Συνυπάρχουσες παθήσεις:ΣΔ Στεφανιαία νόσο, Υπερχοληστεριναιμία

Συμπτωματολογία συμβατή με Σύνδρομο Απνοιών στον Ύπνο: έντονο ροχαλητό, αναφερόμενες διακοπές της αναπνοής στον ύπνο,ημερήσια υπνηλία

Δείκτης μάζας σώματος (BMI): 35 kg/m^2
Υποκειμενική εκτίμηση ημερήσιας υπνηλίας (**ESS**):12

Πολυκαταγραφική μελέτη ύπνου η οποία περιλαμβάνει: ηλεκτροεγκεφαλογράφημα, ηλεκτρομυογράφημα, ηλεκτροοφθαλμιογράφημα, ηλεκτροκαρδιογράφημα, ροόμετρο, οξυμετρία, καταγραφή κινήσεων θώρακα και κοιλίας, θέσης σώματος, κινήσεων ποδιών και μικρόφωνο για το ροχαλητό.

Ημερομηνία διεξαγωγής της μελέτης: 28/11/2016
Ευρήματα:
Διάρκεια μελέτης: 359 min.
Διάρκεια ύπνου: 176 min
Στάδιο ύπνου S1: 6,5 min (3,7 % του ύπνου)
Στάδιο ύπνου S2: 138 min (79,8 % του ύπνου)
Ύπνος Βραδέων κυμάτων (S3+S4): 1 min (0,5 % του ύπνου).
Ύπνος REM: 10,5 min (5,8 % του ύπνου).
Επεισόδια Απνοιών 10,9 /h και Υποπνοιών 60 /h ανά ώρα ύπνου (**AHI: 70,9**)
Επεισόδια αποφρακτικών απνοιών ανά ώρα ύπνου: 8,2 /h, κεντρικών: 0,7 /h και μικτών 2 /h
Επεισόδια αποκορεσμού της αιμοσφαιρίνης ανά ώρα ύπνου (DI: **74**)
Μέση τιμή κορεσμού της αιμοσφαιρίνης κατά τη διάρκεια του ύπνου: 93 %,
Κατά τη διάρκεια των επεισοδίων: 87 %,
ενώ η ελάχιστη τιμή κορεσμού της αιμοσφαιρίνης που καταγράφηκε: 80 %.
Η αντίστοιχη τιμή κατά την άσκηση: 95 %
Μέση καρδιακή συχνότητα: 92 παλμοί το λεπτό. Επεισόδια βραδυκαρδίας 0 και ταχυκαρδίας 1 ανά ώρα ύπνου.

Διάγνωση: Σύνδρομο Αποφρακτικής Άπνοιας του Ύπνου (ΣΑΑΥ) σοβαρού βαθμού

Μελέτη ύπνου υπό συσκευή r-CPAP με στόχο τον προσδιορισμό της θεραπευτικής πίεσης στη συσκευή.
Ημερομηνία: 5/12/2016
Η καλώς ανεκτή πίεση που επέφερε μείωση του δείκτη απνοιών – υποπνοιών (AHI:3), των αποκορεσμών της οξυαιμοσφαιρίνης και βελτίωσε την αρχιτεκτονική του ύπνου ήταν 12 cmH_2O.

Συστάσεις:

Λόγω της μεταβολής της πίεσης κατά την αλλαγή θέσης σώματος κατά την διάρκεια του ύπνου κρίνεται απαραίτητη η χορήγηση στον ασθενή συσκευής auto-n-CPAP στην οποία η διακύμανση της πίεσης θα είναι από **5 cmH_2O έως 17 cmH_2O.**

Ο ασθενής θα πρέπει να χρησιμοποιεί τη συσκευή κάθε βράδυ κατά τη διάρκεια του ύπνου.

Επανέλεγχος σε 2 μήνες

Appendix D

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
«ΑΤΤΙΚΟΝ»
Β΄ΠΡΟΠΑΙΔΕΥΤΙΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΚΑΙ ΜΟΝΑΔΑ
ΕΡΕΥΝΑΣ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΑΘΗΝΩΝ
Διευθυντής: Καθηγητής Γ. Δημητριάδης

ΔΟΚΙΜΑΣΙΑ C-ΠΕΠΤΙΔΙΟΥ (ΤΕΣΤ ΓΛΥΚΑΓΟΝΗΣ)

Ημερομηνία: 23/11/2018

ΟΝΟΜΑ: [redacted]
ΚΛΙΝΙΚΗ:

Χρόνος (min)	Γλυκόζη (mg/dL)	C-Πεπτίδιο (ng/mL)
-20		
0	175	3,20
2	156	2,70
4		
6	179	3,18
10		
15		

ΠΑΡΑΤΗΡΗΣΕΙΣ:.....
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Ο ΙΑΤΡΟΣ