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The Role of Glutathione Administration in the Treatment of Infertility Men

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دور الجلوتاثيون في علاج العقم عند الرجال

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ABSTRACT

Lipid peroxidation negatively affects sperm function by decreasing the number of motile sperm in the reproductive tract, which is caused by a disruption in the balance of sex hormones that regulate male fertility. A total of 80 adult men, aged 36-55 years, participated in this study. The group comprised 40 fertile control men and 40 men with idiopathic infertility who received antioxidant treatment. Among them, 15 men were younger than 36 years and 65 men were older than 36 years. All the infertile men had been married for at least five years and had no children. The study samples were collected from an infertility clinic at Kirkuk Teaching Hospital and private clinics. Each patient received glutathione supplementation once a day for five months, starting oral antioxidant therapy in July and continuing until December 2023, along with garlic taken twice daily with food. Initially, there were slight but significant differences observed in FSH and LH levels between the control group and infertility patients before treatment, while testosterone levels were significantly lower in the infertility group. However, after five months of treatment, there was a significant increase in FSH, LH, and testosterone levels in the idiopathic infertility group compared to the control group. The research indicated a significant increase in seminal plasma glutathione (GSH) and glutathione peroxidase (GPx) and a significant reduction in seminal plasma malondialdehyde (MDA). These changes led to a significant increase in the sperm count of idiopathic infertility men after five months of treatment compared to the control group. Furthermore, FSH levels significantly increased after two months of treatment, with a corresponding increase in serum GSH. Thus, the administration of glutathione with garlic significantly reduced serum MDA and significantly increased serum FSH, total testosterone, and the count of motile sperm in idiopathic infertility men.

Key Words: L-Glutathione250MG , Garlic ,idiopathic infertility men ,sperm count ,total testosterone

الملخص

بيروكسيدة الدهن يضعف وظيفة الحيوانات المنوية من خالل تقليل عدد الحيوانات المنوية المتحركة أثناء الإخصاب مما يؤدي إلى اختلال توازن الهرمونات الجنسية التي تنظم خصوبة الذكور والسعي لدراسة تأثير كبسولة المكملات الغذائية بجرعة250ملغم form free L-Glutathioneمع الثوم على مستوى هرمون التستوستيرون الكلي وهرمون المحفز للجريبات FSH وعلى عدد الحيوانات المنوية المتحركة اثناء الإخصاب ومستوى كلوتاثيون
بيروكسيدزGPx( ) لدى الرجال الذين يعانون من العقم مجهول السبب وأعمارهم تراوحت أكثر من30 سنة، وقد ضمت الدراسة 80 رجلا بالغا، تراوحت أعمارهم بين 55-36سنة، في حين خمسة عشر رجل تقل عمرهم عن 36 سنة، وخمسة وستون رجلا تزيد أعمارهم عن36سنة، و40 رجلا متزوجا عالي خصوبة لديهم أطفال، بينما 40 رجلا قليل الخصوبة عقيم مجهول السبب خاضع للعالج متزوجون لمدة لا تقل عن خمس سنوات وليس لديهم أطفال .تم جمع عينات الدراسة من مستشفى كركوك التعليمي والعيادات الخاصة، حيث تلقى كل رجل عقيم أقراص مكملات كلوتاثيون بجرعة 250ملغم يوميا مرة واحدة لمدة خمسة أشهر عن طريق الفم مع الثوم مرتين يوميا في طعامهم بعد بدء العالج من شهر تموز لحد شهر كانون الأول سنة,2023 وقد لوحظ تغير طفيف ملحوظ بين مجموعة العقم قبل العالجLH(, (,))FSH مع مجموعة السيطرة, في حين انخفض مستوى هرمون التستوستيرون بشكل كبير قبل العالج مقارنة مع السيطرة عند مستوى معنوي أقل من واحد بالمئة، بينما أظهرت الدراسة وجود زيادة معنوية في مستوى هرمون LH (FSH, وهرمون تستوستيرون) بشكل ملحوظ بعد العالج لمدة خمسة أشهر،
لوجود ارتفاع معنوي نسبي في مستوى سيرم كلوتاثيون وكلوتاثيون بيروكسديزفي المصل وانخفاض معنوي عالي في مستوى مالوندالديهايد في المصل بعد العالج لمدة خمسة أشهر. كل هذه المؤشرات أدت إلى ارتفاع معنوي لعدد الحيوانات المنوية المتحركة بعد العالج لمدة خمسة أشهر.
إن تعاطي الجلوتاثيون مع الثوم يؤدي إلى انخفاض معنوي في مالوندالديهايد وزيادة معنوية في مستوى هرمون محفز للجريبات في المصل ، زيادة معنوية عالية لهرمون التستوستيرون الكلي ، مما أدى إلى زيادة معنوية عالية لعدد الحيوانات المنوية المتحركة للرجال الذين يعانون من العقم مجهول السبب.

الكلمات الدالة: كلوتاثيونL250-ملغرام، الثوم، عقم مجهول السبب عند الرجال، عد الحيوانات المنوية،التستوستيرون الكلي

1- Introduction

About 20% all couples affected by idiopathic infertility men and half of them should be oligoasthenoteratospermia(OAT),which was be condition reducing the motile sperm count around ova which causes by reactive oxygen species (ROS) in the spermatozoa that may production from some drugs and obesity ,while the treatment with non- enzymatic antioxidant scavenger the free radicals and reducing them from seminal plasma under limiting lipid peroxidation (MDA) from sperm membrane DNA,

.[1,2] The antioxidant supplementation enhancing maintain the ROS clearance and production balance that increased by leukocyte cells and appears directly consequence of vascular diseases that inducing hypoxia and ischemia in the reproductive tract lead to immature sperm forms during male testicular damaging who have hyper gonadotrophic and hypogonadism should be presented with highly level of FSH and LH concentration and low level of testosterone ,so the level of FSH elevation but number of spermatogonia remain normally lead to the maturation to be very arrest existed in the spermatozoa, because the infertility men have been normal FSH with normal testis volume and remain to be a zoosperm ,therefore the testicular sperm extraction should be technique for choice more focal spermatogenesis [3,4] ,while the life style modification such as losing body weight and leaving the smoking with eating more fruit with vegetable should be inducing rapid fertility expanding, because the type with dosage of antihypertensive therapy and diuretics should be effected on erectile function and must be the clinical marker of hypogonadism during androgen therapy and lead to decreasing total testosterone. (GSH) has been protective mechanism by inhibition the activity of ROS during peroxiding the cellular oxygen metabolism and detoxification oxygen species by GPX which was converte to oxidizing glutathione(GSSG),on the other hand, the oxidized serum GSH was reducing by garlic

and L- glutathione and releasing NADPH and this reaction conjugated by enzyme known S-transverses glutathione ,therefore the catalase plus GPX in testis was highly significantly reduction ROS for idiopathic infertility men .[5,6]The idiopathic condition causes with abnormal semen analysis and fertility sperm could be found in patients with normal semen analysis and men fertility could be improved the conception through sexual action and needed for minimizing contamination the ROS by leukocyte for suspension the spermatozoa of idiopathic infertility men and polyunsaturated fatty acid are present in the linoleic acid which is important for sperm motility with vitamin Ethat present in the garlic with L-glutathione therapy were benefiters.[7,8]

The aim of the study to investigation the effects of(GSH)L-Glutathione 250mg free form sachets was dietary supplementing capsules with Garlic on Total testosterone

,follicular stimulating hormone (FSH) with motile sperm count during fertilization and glutathione peroxidase (GPx) of idiopathic infertility men at age ranged more than 30 years

2- Material &Methods

In this research, the patient has been selected according on the clinical laboratory data with examination should be diagnosing medically and lead to family separation when male partner factor constitute at 20% of cases.

1-2 The participants recruitment

This study included 80 men,40 idiopathic infertility men who were administration of oral glutathione(Reduced L glutathione with vitamin C and Alpha lipoic acid)was china sinoway/GSH ,CAS NO:70-18-8 at dosage 250mg for each infertility men and they were married more than three years no children, while less than 4ml semen analysis was done during 2-5 months for treatment each infertile patient before complete conclusion and the sperm count from semen specimen which

collected from all subject after less than 5 days for determination the sexual hormones from sterile container, and 40 men healthy control when age ranged 36-55years for all subjects which included in this study and all them eating garlic with these food .Exclusion criteria genetic diseases and factors affecting on lipid peroxidation such as alcohol and drugs with metabolic syndrome such as insulin resistance with hypertension and hyperlipidemia with atherosclerosis ,while the control group included healthy men have offspring one or more child and data questionnaire about age and sexual history with lifestyle and diet within psychosocial condition. The sample size for this study was collection from 40 infertility men and 40 healthy control, while inclusion criteria was taken from all subjects.

2 -2-Blood collection

The fasting venous blood sample was obtained from research men and putting in the plain tube and allowing for clotting at room temperature at25C0 for one hour, and serum sample was separated by centrifugation at 3000 rpm for 15 min then transferred by micropipette and dividing in to six equal fraction in six test tube and fraction for each parameter and the sera stored at -20C0 until time of analysis the serum for measuring the level of LH with FSH and testosterone within MDA and GSH within GPx by Beckman culture assessment by two electron chemiluminescenc immunoassay{ ECLIA}.

2 -3-sperm count

The liquid semen was centrifugation at 300Xg for 10min at room temperature and the remaining is sperm at volume about 1ml was washing timely in 3ml of medium

HEPES-buffer human tubular fluid {HTF} and this medium supplementation with human serum albumin used for washing the sperm afterward 0.5ml of medium was addition to the suspicions of falcon tilted at 450 angle and incubation at 37C0 at until 45min,so the falcon then placing in the

vertical position for measuring sperm count on flowing cytometer and sperm was counted using Neubauer chamber and normal sperm count at adult men more or equal to the 39X106 [9,10].

2 -4- MDA estimation

Lipid peroxidation measuring by reaction with thiobarbituric acid {TBA} and the result of MDA to GSH adduction was extraction with n-butane and the fluorescence in the organic layer was determined due to taken semen sample and prepared by suspending them with tries citric acid buffer at ph7.4 and TCF , 05mM and the final volume at 0.4ml, which using of MDA in the semen and comparing the fluorescence intensity of

sample when equivalent formed in the present the 1,1,3,4- tetramethoxypropane, so the result was expressed in mmol/l seminal plasma.[11]

2 -5- GSH estimation

Serum glutathione was measuring by thiol level according to Elman's method which is scientific basis principle and depending on reaction of S.S Dithiolois {2-nitrobenzioc acid within aliphatic thiol compound at pH 8 for producing one mole of p-nitrothiol phenol anion per mole thiol, this anion highly colored and measuring the thiol concentration which represented GSH level[12.[

2 -6-serum FSH,LH estimation

Serum determination of FSH and LH could be measuring by using ELISA, so the ELIZA kit was producing by Moonblind (U.S.A.) by using test procedure with protocol recommended by the kit manufacturer was giving in detail of the kit’s and insert for FSH & LH and medium range 2.5 ,5.4 IU/L.[13,14]

2 -7- Total testosterone estimation

serum testosterone level for all male patients with infertility and healthy control was measuring by using enzyme-linked immunosorbent assay(ELIZA) method. The ELIZA kit was using and manufactured by Bio-Check- Inc.when median range 3.9ng/ml company (USA),so this test procedure and protocol recommended by the kit manufacturer and adopted which was giving in details of the kit's insert.[15]

2 -8- GPx estimation

The extracting and assays done for measuring the GPx level according to Sigma Aldrich technical bulletin Glutathione Assay by Kit/Catalog Number CS0260/ 2011 year catalogue.[16]

2 -9-Stastically analysis

Sperm concentration and serum sex hormones concentration should be evaluated before and after5 months of the research and the statistical analysis system was used for difference factors (group) in the research parameters and the significant difference test at the comparative between means at $P \leq 0.05$.[17]

3- Results & Dissections

In the first part of this work which aimed to identify the biological role of GSH therapy for sperm cell under reducing MDA levels which inducing the oxidative stress, since the GPx should be the main determination for adaptive response of ROS and this study hypothesized the GPx should be the pharmacological inhibitory of the ROS damaging with sperm, the total 80 adult men who visiting Kirkuk teaching hospital and private

clinics and participant at two groups(Table1) infertility40men using antioxidant therapy and fertility control men has more than 80million/ml sperm in the semen and age ranged 36 -55years with duration of married more 5years ,when 15 men less than 36years and 65 men larger

than36years,there is significantly difference between sperm count of fertility(88.6±8.7) and infertility group(61.7±4.32 X106/ml),while highly significantly decreased the total testosterone of infertility men(3.33±0.3) compared with control fertility men(5.76±0.8 ng/dl),but the concentration of FSH with LH slowly decreasing of infertility men(3.43±0.8 mlu/ml , 5.26±0.9 mlu/ml)compared with fertility men(5.49±0.9, 8.29±0.7 mlu/ml),while the level of serum GSH significantly decreased of infertility men(8.93±0.44)than control fertility men(31.5±5.35mmol/l),but GPx decreased of infertility (24.88±8.66)than control(43.38±4. IU/L)at $p<0.05$,so serum MDA significantly increased of infertility men(8.89±0.9) than control men(4.21±0.55mmol/l), The treatment by antihypertensive drugs such as captopril and amlodipine with mobile phone using more than 5hours daily and overweight more than 34kg/m2 may be decreasing hormone testosterone biosynthesis and drooping motile sperm at 45% after damaging with ROS during hyperthermia of men patient who have hypertension more three years ,then lead to decreased motile sperm during fertilization(fig1) because this hormone very important for spermatogenesis, while the level of FSH and LH not highly decreasing of infertility men by oral GSH(L- Glutathione 250mg that content vitamin C with alpha lipolic acid and supplementation with garlic) that has been rich with vitamin C,B,E and Zink in them nutrition should be improved the sperm quantitatively and physically ,then could be protected the lipid peroxidation of sperm membrane then lead to collusively disorder sperm around the ova during conception and this result agree with[18],this finding shows the level of FSH & LH not highly evaluation during early treatment for stopping these development and functions ,but highly decreasing hormone testosterone level with hypogonadism in idiopathic infertility lead to decreasing sperm count.

Table (1): level of sperm count ,FSH ,total testosterone ,LH before treatment and control group

parameters	Infertility group n=40	Control group n=40	t-statistic	SE	LSD	P value
Sperm count(X10^6/ml)	61.7±4.32	88.6±8.7	15.276	2.094	31.980*	<0.0001
Serum FSH(mlu/ml)	3.43±0.8	5.49±0.9	3.148	0.197	0.620*	0.0028
Serum testosterone(ng/dl)	3.33±0.3	5.76±0.8	15.802	0.402	6.360*	<0.0001
Serum LH (mlu/ml)	5.26±0.9	8.29±0.7	12.254	0.632	7.750*	<0.0001
GP x seminal plasma(IU/L)	24.88±8.66	43.38±4.69	1.190	1.436	1.710	0.2397
MDA seminal plasma (mmol/l)	8.89±0.9	4.21±0.55	-20.646	0.173	-3.580*	<0.0001
GSH seminal plasma(mmol/l)	8.93±0.44	31.5±5.35	2.876	0.154	3.320*	0.006

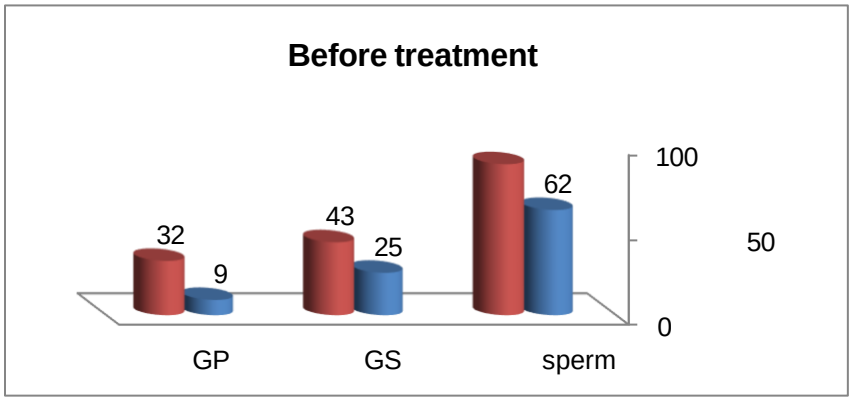

Figure (1): level of antioxidant of control(red) and infertility men(blue) in the sperm count p<0.001 Decreased antioxidant levels lead to impairing sperm count for infertility men

Table 2 shows the mean sperm count of idiopathic infertility men which has been highly significantly increased after5month treatment by GSH therapy with Garlic(98.97± 3.4)

than 2months treatment(69.99±9.9 X106/ml)for increased hormone testosterone after5month(18.96±0.9)than infertility group after 2month(12.6±1.8 ng/dl)which has been major role of sperm function ,so the level of GPx highly increased significantly after 5month treatment(35.2±3.2)than 2months treatment(33.49±6.93 IU/L) ,which was be main detector for significantly depletion serum MDA after 5month treatment(3.38±0.86) compared 2months treatment(6.88±0.11mmol/l),but serum GSH slowly changed after 5month treatment(22.75±4.55

)than 2month treatment(19.43±3.55mmol/l)which important indirectly for elevation FSH with LH that are increased after 5month treatment significantly(9.54±0.4, 23.6±2.6mlu/ml) than 2months treatment(8.92±0.9, 15.85±2.38),therefore ,the level of Total testosterone decreasing for infertility men may be due to negative feedback of testosterone action on hypothalamic pituitary system after response to vasodilation prostaglandins ,but the GSH therapy with garlic increased the concentration of glutathione peroxidase GPx that has been protective effected on ROS for increased tail beat attribution for the sperm after 5months treatment ,therefore poor absorbance of supplementation GSH and garlic from intestinal tract could be impacted the therapeutic out comes and significantly reduced the GPx for infertility men after 2months treatment compared with infertility men after 5months treatment when the endogenous antioxidant protective lipid peroxidation for sperm due to scavenging the ROS for hydrogen peroxide{H2O2},which has been confer protection for the lipid peroxidation MDA and enhancement sperm motility with quantity forward testosterone secretion's ,agree with,[19] shows the GPx increased the activity of sperm for elevation the spermatogenesis of oligozoospermia and the study diagnosed the lower cellular antioxidant protection GSH with GPx lead to sperm vulnerably to ROS in these membrane due to both enzymatic and non-enzymatic antioxidant have been protective effected for harmful and then decreasing the level of plasma GSH with GPx for response to scavenger MDA to be increased and agree with[20],shows the hypertension was significantly implication during oxidative stress and reducing antioxidant action lead to testosterone altering from Leydig cell. The hormones FSH ,LH and testosterone when they energizing after 2months treatment should be very useful for management the male infertility when these hormones increased after 5months treatment compared with infertility groups after 2months treatment lead to elevation the severity of seminiferous epithelial destruction ,agree with[21]showing this antioxidant may be reduction

sperm DNA fragmentation and apoptosis ,so the increased of FSH,LH with testosterone after 5months treatment has been directly disturbance the Leydig cell and seminiferous tubules of infertility men ,and these hormones have been biological imbalanced for gonadal-pituitary feedback due to didn't allowing the germ cell damaging with ROS finality [22],while elevation LH after 5months treatment infertility men compared with infertility groups after

2months treatment(fig2) may be from increased the secretions of testosterone from Leydig cell, and this result agree with[23] who suggested the present HCG lead to increased LH which is good reason for FSH suppression.

Table (2): level of Total sperm count ,FSH, total testosterone,LH after treatment by orally GSH(250mg)sachets

parameters	After 2months treatment n=40	After5months n=40	P value
Sperm count($X10^6$/ml)	69.99±9.9	98.97± 3.4*	<0.0001
Serum FSH(mlu/ml)	8.92±0.9	9.54±0.4*	=0.003
Serum testosterone(ng/dl)	12.6±1.8	18.96±0.9*	<0.0001
Serum LH (mlu/ml)	15.85±2.38	23.6±2.6*	<0.0001
GP x seminal plasma(IU/L)	33.49±6.93	35.2±3.2	0.249
MDA seminal plasa(mmol/l)	6.88±0.11	3.38±0.86*	<0.0001
GSH seminal plasma(mmol/l)	19.43±3.55	22.75±4.55*	=0.007

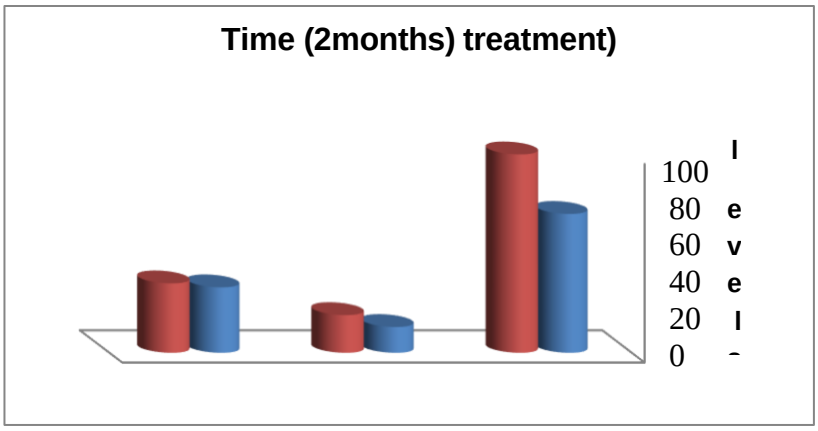

Figure (2): level of testosterone and GPx of infertility men in the sperm count after 2 months(blue)& 5months(red)treatment p<0.001 ,reducing of glutathione peroxidase level obtain of infertility men after motile sperm elevation.

Table3 shows the sperm count(98.97± 3.4 X106/ml) evaluation significantly after 5months treatment by orally GSH with garlic than control groups at p value<0.0001 due to significantly increased LH(23.6±2.6 mlu/ml) concentration after 5months treatment than control group, when improved the level of GPx(35.2±3.2 IU/L) significantly increasing after 5months treatments with FSH(9.54±0.4 mlu/ml

(compared with control groups. While the MDA(3.38±0.86mmol/l) decreased significantly after 5months treatment compared with control groups,all these data enhancing elevation level of testosterone(18.96±0.9ng/dl) significantly after 5months treatment. The results showing the treatment by administration 250mg orally GSH for 5months with garlic increased testicular function significantly represented by motile sperm count and level of FSH,LH with testosterone which has been protective effects of oxidative stress for infertility men and agree with[24],who suggested this antioxidants compensate the losing of sperm cytoplasmic enzyme and extruded it during spermatogenesis ,while the decreased of MDA seminal plasma and increased serum GSH concentration of infertility men after 5months treatment with garlic should be reflected for increasing the antioxidant capacity represented by GSH therapy with serum GPx and decreasing MDA after 5months treatment(fig3) due to detoxification the cytotoxic effects of aldehyde formation by lipid peroxidation and lead to increased motile sperm within viability then inducing obtaining the MDA level significantly decreasing and influencing sperm activity through elevation of GSH with GPx levels which is acts as better indicator for male reproductive function represented in the sperm function and complication infertility with severity of inflammation may be increased temperature from2C0 at 4 C0 more than 5months and disruption the spermatogenesis, and the low testosterone level should be risk marker for cardiovascular disorder and the antihypertensive drugs induce sperm infusion[25] who suggested the ROS in hypertensive patients lead to depletion of

free glutathione level in the testis and epididymis and GSH with garlic inducing expression antioxidants enzyme increased in testis such as GPx with glutathione redacts GR. .

Table (3): level of Total sperm count ,FSH, total testosterone,LH after treatment and control group

parameters	Control group n=40	After5months n=40	t-statistic	SE	LSD	P value
Sperm count($X10^6$/ml)	88.6±8.7	98.97± 3.4*	5.551	1.868	10.370	P<0.0001
Serum FSH(mlu/ml)	5.49±0.9	9.54±0.4*	20.561	0.197	4.050	P<0.0001
Serum testosterone(ng/dl)	5.76±0.8	18.96±0.9*	54.810	0.241	13.200	P<0.0001
Serum LH (mlu/ml)	8.29±0.7	23.6±2.6*	28.430	0.539	15.31 0	P<0.0001
GP x seminal plasma(IU/L)	43.38±4.69	35.2±3.2	-4.065	0.204	-0.830	P=0.0001
MDA seminal plasma(mmol/l)	4.21±0.55	3.38±0.86*	-4.065	0.204	-0.830	P<0.0002
GSH seminal plasma(mmol/l)	31.5±5.35	22.75±4.55*	-6.229	1.405	-8.750	P<0.0001

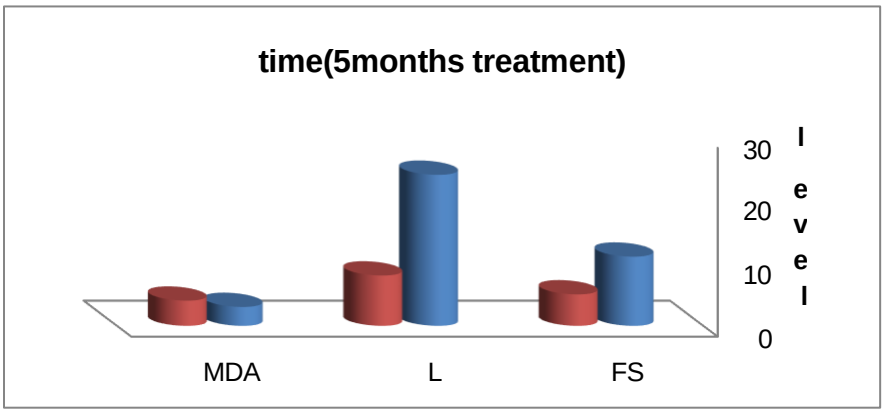

Figure (3): level of sex hormones in the MDA estimation p<0.001 for control(red) & infertility men(blue)5months therapy,treatment by orally GSH enhancement LH secretions and inhibition lipid peroxidation MDA for infertility men

4- Conclusions

About over 20% of all men infertility causes in Kirkuk city idiopathic ally due to effectiveness by some drugs such as antihypertensive drugs(ACEI)with obesity from lifestyle and the sperm count with total testosterone should be the only clinically test could be diagnosed 15-20 men who have less sperm function during fertilization ,so the L-Glutathione therapy at dosage250mg daily within garlic after 5month treatment could be increased the fertility through increased survival the sperm to reproductive tract from facultative antioxidant action of them during improved GPx activity which augmented LH secretions that could be abounded motile sperm through reproductive tract.

5- Suggestions

This study suggested to investigation for scope other antioxidant administration such as carnitine within selenium and vitamin B-complex within ginger with oral glutathione for minimizing the men infertility prevalence for selected population ,other elements could be effected on sex hormones such as vitamin D and A within the zinc have been mediated effectiveness on steroid hormone and progesterone within androgen hormone, therefore, we suggested proceeding researches about this elements' with TSH hormone that has been profile role for male reproductive system ,anther suggested by pilot study for emphasizing information about seminal leukocyte which is may be the main source for ROS of the sperm at ejaculation infertility men.

6- Acknowledgment

We adducing thankfully and appraising for all ministries with universities and workers with coworkers in Iraqi country and Kirkuk city and Kirkuk university who help me to made this research good possible.

7- Abbreviations:

FSH: follicular stimulating hormone

GPx: fertilization and glutathione peroxidase LH: luteinizing hormone

GSH: glutathione

HCG: human chorionic gonadotropin ROS : reactive oxygen species

MDA: malonialdehyde TSH:thyroid stimulating hormone TBA: thiobarbituric acid

ELIZA: enzyme-linked immunosorbent assay ACEI: angiotensin converting enzyme inhibitors

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