ISSN: 2617-2070 (Print); 2617-2070 (Online)
Journal of Advanced Sciences and Engineering Technologies
Available online at: http://www.jaset.isnro.org

Journal of Advanced Sciences and Eng. Technologies
JASET

Investigation on Glucose and levels of Zn and Cu in Sera of Iraqi Males addicted on Methamphetamine or Tramadol

Rulla Sabah,Ahmed saad abbas Fatin F.Al-Kazazz ; Salam A.H. Al-Ameri

Chemistry Department, Faculty of science, Al Mustansiriyah University, Iraq

Rulla_Sabah_2004@yahoo.com

Keywords

Addiction, methamphetamine, tramadol, chronic disease

A R T I C L E I N F O

ARTICLE INFO

Article history:

Received 01 October 2020

Accepted 18- November -2020

Available online 27– November 2020

DOI: http://dx.doi.org/10.32441/jaset.03.02.06

A B S T R A C T

Addiction is the most critical form of Addiction. It is a chronic disease with a potential for fatality if not treated. In this work, 180 samples of male individuals were collected in this study. They classified into three groups, groups: G1 who were healthy control; G2 who was addicted to methamphetamine (meth); G3 who was addicted to tramadol (Tra). Each group consists of 60 heavy smokers' Iraqi male individuals in the age range of 18-43 years. The results showed a highly significant increase ($p<0.0001$) in the level of Glucose of the two addicted groups in comparison with the healthy group. A highly significant decrease ($p<0.0001$) could be seen in the level of Zn of the two addicted groups G2, G3 compared to the control group, while the level of Cu of the two addicted groups were highly significant increased ($p<0.0001$). Also, the results showed a highly significant difference ($p<0.0001$) in BMI for the studied groups, G2, G3 in comparison with the control group. All addictive individuals under this study were at normal weight depending on their BMI.

Introduction: Addiction

Addiction is defined as a chronic, mood disorder classified by two Types of Addiction, substance Addiction for example alcoholism, drugs abuse and smoking, behavior Addiction for example gambling, spending, eating, social media and sexual activity. Drugs Addiction is the most critical form of Addiction. It is a chronic disease with a potential for fatality if not treated. It is called pain-killing drugs due to their action is blocking the signal of pain between nerves in the body (1). Addiction compounds included morphine, codeine, heroin, methamphetamines (meth), amphetamines, cocaine, Tramadol (Tra) and marijuana (2). Serious widespread medical and health consequences associated with drug abuse (Psychoactive drugs) involve neurotoxicity, cardiovascular complications, impairment of the immune system function, and many other physiological effects (3). Drugs alter the way people think and behave by disrupting neurotransmission in the brain (4). Endorphins and enkephalins are substances secreted by the brain to relieve the pains of the human body, they are similar in composition to opioid derivatives. It makes significant changes in the functions of the body organs by influencing the workings of the brain cells. This effect is done with the help of the neuro- mediators, which are formed from the amino acid (Tryptophan and tyrosine) noradrenaline, adrenaline, dopamine, serotonin, acetylcholine and histamine whom transfer the psychological effects that affect the work of cells, especially in the synapses (4). Some drugs influence by the pharmaceuticals that increase or decreasing or even inhibiting biological reactions. The neurotransmitters or vectors would interact with the receptors forming a complex. The receptors that are loaded by the vectors interact directly with the nervous system. Neurotransmitters are divided into the nervous system according to the kind of competition between them and the control returns to the strongest. Which prevents the movement of substances (5).This explains why the consumption of a variety of drugs on the basis of and the existence of two types of receptors on the nerve cell wall membrane is an active receptor interaction with the drug leads to the effect of the drug, and static and inactive receptors do not interact with the drug, but drugs continuously lead to the activation of static receptors that become active receptors, leading to the need for the individual to increasing doses of the drug to cause the same effect, which was caused by low doses in the previous

Some Parameters Related to Addiction

1.Glucose Levels.

Glucose is the main source of energy for the cells of the body. Hormones in the body aid-controlled glucose level in the blood (6). Use medications such as heroin, methadone, meth and morphine are all linked with hyperglycemia, also it has been found that codeine causes the same effect (7,8). Methamphetamines and other abused drugs are very dangerous for addicts, especially who have diabetes because this drug would alter insulin activity and production hormone due to the release of too much glucose in the blood leading to a loss of appetite, and depression, (9). Sweet foods are associated with the acute linking of the endogenous opiate B-endorphin in the brain that reduces encephalin mRNA production that may be a result of increased μ-opioid receptor against. There is some evidence that μ-opioid against related to sweet food ingestion may have clinically analgesic functions. Clinically,

sucrose is often given to preterm infants in neonatal to provide analgesia for heel stick for blood sampling (10). This practice is based on evidence that sucrose solutions and artificial sweeteners administered orally reduce screaming and heart rate in children with heel pricks, that the sweet taste of sucrose or sweetener contributes to analgesia, not the sugar itself (11). This effect of opioid sweeteners is also due to the fact that infants born to methadone-dependent mothers did not have the analgesic response because these infants were born with tolerance to the mu-opioid as a result of methadone chronic exposure (10,12)

2.Trace Elements Zinc and Copper

Zinc is the second most important trace element in the human body after iron which has a catalytic and structural role as a co-factor in Cu-Zn superoxide dismutase, it is also necessary for the antioxidant defense (13,14). In the central nervous system (CNS), zinc works at the post-synapse level and influences synaptic plasticity, hormone release and nerve pulsation transmission, and plays an important role in the figuration and repair of the post-synaptic density structure, a network of proteins that connects the neurotransmitter receptors with the intracellular signaling system and the cytoskeleton. (15). The highest amount of zinc in the body exists in the brain in a part called the hippocampus as metalloproteinase, a concentration of zinc of 10 - 300 μM can produce by activation of the zinc-enriched fiber synapses (16), also it has a neurotoxic effect when released at very high concentrations (17). Zinc deficiency may lead to depression symptoms, Attention Deficit Hyperactivity Disorder (ADHD), learning and memory problems, seizures aggression and violence (18). Zinc has been a low concentration in the sera for those who were suffering from depression. This meant the more depressed that means, lower in zinc level which is a depression biomarker, Zinc supplementation in humans has been shown to have antidepressant effects, which indicated that effective antidepressant therapy should be accompanied by increasing the Zn levels in serum. Reduced zinc related to DNA damage increased inflammatory condition (19) and performed as a decreasing factor for malignant tumors expansion, through its role as antioxidant, disorders related with CNS impaired function such as behavioral changes, emotional instability, anxiety, aggressively, irritability (20,21), socializing problems, impaired memory, and learning, neurosensory changes, and anorexia (22,23). Zinc has an important function on mechanisms involved in opioids addiction which occurs at the level of the opioid receptors. Normal physiologic zinc concentration prevents the binding of specific agonists to μ-receptors, while the δ and κ receptors were resistant to this type of inhibition, Fowler el al, proves that the inhibition is determined by zinc ions on ligand-binding to μ-receptors and also by the amino acids which existing on the receptor's structure which is responsible for it (24) . Copper (Cu) plays a significant function in human metabolism, it is fundamental for keeping the strength of the skin, blood vessels, and connective tissue in the body. A Cu perform an important role in the manufacture of myelin, melanin and it is keeping thyroid gland and neurologic systems functioning normally (25). Copper can act as an antioxidant and a pro-oxidant. Free radicals happen naturally in the body and it can harm cell walls, and react with genetic items, and participate in the increase of health problems and diseases. As an

antioxidant, Cu neutralizes free radicals and may reduce or help prevent some of the damage of them which may cause (26). At some times when copper acts as a pro-oxidant, it will raise free radical damage and it causes the development of Alzheimer's disease (27). It is important to Maintain the suitable dietary balance of Cu, along with other minerals such as zinc and manganese. There is a particular degree of contrariness between zinc and copper at the level of biological function that zinc deficiency has more clearly in abuse addicts, as decreased zinc in serum and increased intraerythrocytic copper in heroin users (28,29).

3. Anthropometric Measurements

Anthropometric is a measurement body of the human in terms of the dimensions of adipose tissue, muscle and bone. It is essential to measure subcutaneous adipose tissue because individuals with great values are described to be at enlarged risks for diabetes mellitus, hypertension, gallstones, arthritis and cardiovascular disease and some forms of cancer (30) including values of age, body mass index (BMI), waist circumference (WC), waist to a height ratio (WHtR) Height and weight scales respectively. Waist and hip circumferences were measured with a measuring lap placed 1cm below the umbilicus and at the iliac crest, respectively Body mass index (BMI) was calculated as in the following equation (31) BMI (kg/m2) = weight kg / height m^2 Waist-to-Hip Ratio (WHR) was calculated by dividing waist (cm) to hip (cm) WHR=waist (cm)/Hip (cm) (32) Waist-to-Height Ratio (WHLR) was calculated by waist (cm) to height (cm) WHLR= Waist (cm)/High (cm) The normal range of BMI was reported between 18 to 24.9 kg/m2, while lower than 18.5 kg/m2 suggested that the person is underweight, and with BMI between 25-29.9 kg/m2 was categorized as overweight and those having BMI 30 kg/m^2 or more were categorized as obese persons.

4 Subjects, Material

All the addicted groups were collected from the Ibn-Rushed Hospital and toxic laboratory in the Forensic Medicine Department, from one year 1st June 2018 to 1st June 19, 2019, 180 Iraqi male individuals divided into 60 ones addicted to methamphetamine and the 60 others addicted to Tramadol. A detailed history was obtained from each one. sixty (60) non-addicted healthy subjects serve as the control group participate in this study and they judge to be healthy according to their history and physical examination. All individuals were heavy smokers Exclusion criteria were any disease e.g. diabetic, blood pressure, retinopathy, neuropathy, cardiopathy, and any inflammation that was registered for any subjects under this study.

5.Methods:

5.1 Determination of Serum Glucose

Principle:

The concentration of serum glucose was calculated using a colorimetric enzyme method using a Biosystems kit (GOD-POD) (178).

5.2 Determination Serum trace elements (Zn and Cu)

Flame atomic absorption spectrophotometry was used of trace elements measurement in the serum. Hallow cathode Lamp (HCL) made of the same metal to measure this light that passes through the flames containing free metal atoms that absorb part of the light

intensity reaching the recorder is directly proportional to the concentration of free atoms in the flames reflecting the concentration of the metal in the solution. Dilution of one milligram per litter (10 ppm) of Cu or Zn stock solution with deionized water to achieve the following concentration of zinc and copper standard solution 0.0; 0.4; 0.8; 1.2; 1.6; 2 ppm.

Results and Discussion

The results for fasting serum glucose (FSG) listed in ***Table 1***, It's levels for the three studied groups (G1,G2,G3) were recorded at (5.018±0.4808mmol/L),(9.654±0.934mmol/L), (7.327±0.6238mmol/L) respectively.The results revealed a high significant difference ($p<0.0001$) among all the studied groups, group addicted on Meth (G2) show a high significant increase ($p<0.0001$) in compare with the two other groups G3, G1(the addicted on Tra group and control group) ***Figure 1***. At the same time, a high significant increase ($p<0.0001$) in FSG level was noticed between Tra addictive and control group.

Table 1. The level of Fasting Serum Glucose for the three groups G1,G2,G3 .

Groups	Fasting Serum Glucose (mmole/l)			Table Column Head		
	Mean±SD	SE	p-value	Table column subhead	Subhead	Subhead
Control (G1) N=60	5.018±0.4808	0.08778	0.0001[a]	More table copy[a]		
Addicted on Meth (G2) N=60	9.654±0.934	0.1705	0.0001[b]			
Addicted on Tra (G3) N=60	7.327±0.6238	0.1139	0.0001[c]			

a: p value between G1vsG2vs G3 , b : p value G1vs G2 , c : p-value G1 vs G3

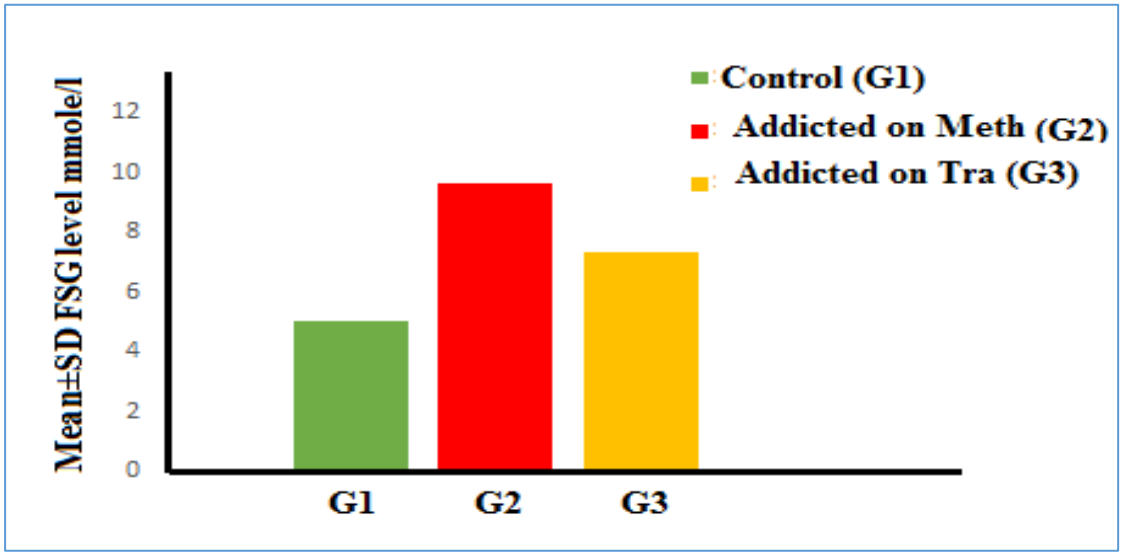

Figure 1 Values of serum Glucose for the studied groups.

These results in this study agree with other study that found an increasing in both fasting serum glucose and fasting insulin levels in opium addicted rabbits, their FSG was significantly higher compared to that of the non-addicted ones (33). In a study conducted on conscious dogs, intravenous morphine infusion had dual effects, low dose (2 mg / h) did not change blood glucose, but high doses (8.16 mg / h) induced hyperglycemia following increased glucose production in the liver and decreased peripheral glucose clearance These results were due to increased epinephrine levels, glucagon. Such effects were also observed due to the increased opioid amount. In addition, the increased use of glucose and the reduction of hepatic gluconeogenesis following activation of peripheral opioid μ-receptors and modification of the genes involved in the metabolism of glucose are among the suggested mechanisms (34). The reduction of two-hour postprandial glucose in diabetic addicts. It may be due to reduce gastric emptying due to activation of the μ-opioid receptor and subsequently delayed intestinal glucose absorption (35). In addition, the presence of underlying diseases and likely effects of medicinal products taken by the subjects may also come into play. In some studies, hyperinsulinemia and impaired glucose metabolism were close to what occurs in type 2 diabetes, despite normal levels of glucose in opium addicts (36) When experimenting with mice, researchers found that brain circuits that play a role in the search for food may interfere with those key factors in drug use. The researchers also found that The food and drugs administration (FDA) approved drugs for the treatment of obesity and diabetes, which activates receptors called peptide-like peptides similar to cocoons (GLP-1), can reduce the desire to search for cocaine, thus reducing relapse after quitting take drugs. The hormone (GLP-1) is a hormone secreted in the body as a natural reaction to eating meals, to maintain the balance of glucose, and this hormone lowering the level of glucose in the blood by stimulating the secretion of insulin from beta cells in the pancreas, and reduces the movement of the intestine. The results showed that those drugs significantly reduced the passion. Mice that have been

addicted to cocaine and narcotic drugs - in the search for drugs, as well as reduced rates of relapse and withdrawal symptoms after taking off drug use Although drugs may temporarily reduce blood pressure, they only increase blood glucose and most blood fats. Moreover, its long-term use has negative effects and therefore worsens diabetes, blood lipid abnormalities and high blood pressure. (37,38). The present study proved that addiction on Meth or on Tra would increase the serum glucose level and the Meth is more effective than the Tra in occurring hyperglycemia for addiction on them. In the other hand it was noticed that this increase in glucose level is affected by increasing the duration of addiction and the dose of drugs

Comparison of Trace Element (Cu and Zn) in Addicted people and Controls

In Comparison of trace elements between addicted groups (G2 ,G3) and control group (G1) the result indicates that there was a high significance difference between the studied groups (p=0.0001) for each of Zn , Cu and the Cu/Zn as shown in *Table 2*

Table 2. The value of Zn, Cu and Cu/Zn

parameter	**Control (G1) N=60**	**Addicted on Meth N=60 (G2)**	**Addicted on Tra N=30 (G3)**		Table Head	Table Column Head		
	Mean±SD	**Mean±SD**	**Mean±SD**			Table column subhead	Subhead	Subhead
Zn	**0.5023±0.05624**	**0.204±0.03201**	**0.2421±0.0338**		copy	More table copy[a]		
Cu	**0.6905±0.0563**	**0.8893±0.0458**	**0.8338±0.0525**					
Cu/Zn	**1.389±0.641**	**4.489±0.8858**	**3.535±0.7065**					

p-value were 0.0001 for all groups

Zinc acts at the post-synapse level within the central nervous system (CNS) and influences synaptic plasticity, hormone release and nerve impulse transmission (39). The brain is one of the organ s with a high concentration of Zn+2, since it contains about 1.5% of the estimated 2 to 3 g of zinc in the human body (40). Research of both humans and animals have shown reduced serum zinc under conditions of opioid administration. (41). A very important component of zinc behavior on mechanisms involved in opioids addiction takes place at the level of the opioid receptors, Physiologic zinc concentration inhibits the binding of multiple agonists to μ-receptors; δ and κ receptors were fairly resistant to this form of inhibition (42). Another research demonstrates the inhibition determined by zinc ions on ligand-binding to μ-receptors and identifies the amino acids that are responsible for it in the receptor structure. Such agonist binding inhibition entails a decline in both receptor affinity and binding sites and is due to the interaction of zinc with essential SH-groups in the opiate receptor structure. In brain sites, the hippocampus has high zinc contents (43).

Also in the present study, It observed that the addicted persons G2, G3 have declined the Zn concentration and raised Cu concentration in serum in comparison to control group (G1). It is very important to calculate Zn/Cu ratio which is essential for proper of human organism and clinically more sensitive and reliable marker than determination of either of these trace metals (44). because Zn can complete with Cu in the small intestine and interfere with its absorbance (45). A though Cu and Zn have an important role in functioning of CNS and associated with neuropsychiatric disorders (39). Also it noticed that the conc of Zn in Addictive persons G2, G3 was decreased compared with control group (G1). Serum Zn conc in Meth users(G2) were reported to be lower than the Tra users (G3). At the Same time Cu conc in Addictive persons (G2, G3) was increased compared with control group(G1). Serum Cu conc in Meth Addicts(G2) was higher than Tra Addicts (G3) . In the other hand it noticed a increasing in the value of Cu/Zn ratio by increasing both the duration of addiction and the dose of drugs.

Anthropometric Measurements

The mean ±SD values of age, body mass index (BMI), waist circumference (WC), waist to a height ratio (WHtR) and Age percentage for all the studied groups, ***Table 3.***

Table 3. Demographic characteristics of the four groups under study

	G1	G2	G3
Parameters Age(year)			
	27.87±6.078	27.4±6.284	28.43±6.69
19-29 years	28(46.6%)	27(45.0%)	28(46.6%)
30-40 years	22(36.7%)	22(36.6%)	22(36.7%)
41-50 years	10 (16.7%)	11 (18.4%)	10(16.7%)
BMI kg/m^2	21.5±1.158	18±1.493	20.01±1.89
WC(cm)	83±4.23	72±1.196	75±2.029
WHtR	0.462±0.022	0.401±0.05	0.4218±0.01

Control G1 (60), Addict on Meth (G2) N=60, Addict on Tra (G3) N=60, BMI: body mass index, WC: waist Circumference, WHtR: Waist to height Ratio.

It was reported that the risk factor in subjects increased about seven times than healthy weight, also it increases by a threefold with overweight subjects (46). On the other hand, it was found that the distribution of body fat considers an important factor of increased risk of diseases . Most addicts lost their jobs and had to pay extra costs to get their drug, which resulted in malnutrition and vitamin deficiency for the opioid users. (47). Divsalar et al, Found that the use of opioids suppresses appetite and reduces weight in many cases,

therefore, in some studies the reduction of lipids may be due to weight loss or nutrient deficiency not due to the direct effect of opium (48) .

References

[1] Volkow. N; Boyle. M. (2018). Neuroscience of Addiction: Relevance to Prevention and Treatment. American Journal of Psychiatry, 175(8):729-740. doi: 10.1176/appi.ajp.2018.17101174

[2] Farisco. M; Evers. K; Changeux. J,(2018), Drug Addiction: From Neuroscience to Ethics. Frontiers in Psychiatry, 9:595-609 . doi: 10.3389/fpsyt.2018.00595

[3]Gramlich. J ,(2018), "Nearly half of Americans have a family member or close friend who's been addicted to drugs". Pew Research Center.

[4]Taylor .SB; Lewis .CR; Olive MF ,(2013),"The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans". Subst. Abuse Rehabil. 4: 29–43.

[5]Perry .CJ; Zbukvic. I; Kim .JH; Lawrence .AJ (2014). "Role of cues and contexts on drug-seeking behaviour". British Journal of Pharmacology. 171 (20): 4636–4672.

[6] .Lehninger .A; Nelson .D; Cox .M ,(2017), Lehninger Principles of Biochemistry (7th ed.). New York: W.H.Freeman. p. 930.

[7] Miller, Shannon C.; Fiellin, David A.; Rosenthal, Richard N.,(2018), Principles of Addiction Medicine. 6th eddition, Philadelphia: Lippincott Williams & Wilkins;. pp 127-131.

[8]Dey.PK;Feldberg's.,
(1975) ,Hyperglycemia produced by drugs with analgesic properties introduced into cerebral ventricles of cats. British Journal of Pharmacology. Vol 54: 163–170. [PubMed:1148506]

[9] Sanli. D. B; Bilici. R.; Suner. O; et al , (2015), Effect of different psychoactive substances on serum biochemical parameters. Int. J. High Risk Behav. Addict.J, Vol 4: 1–5.

[10] David .J ;Mysels; MBA1 ; Maria. A ,(2011), The relationship between opioid and sugar intake: Review of evidence and clinical applications , J Opioid Manag. Vol; 6(6): 445–452.

[11] Ramenghi.L.A; riffith .G.C; Wood.L.A; Levene .M.E. ,(1996), Effects of non-sucrose sweet tasting solution on neonatal heel prick responses. Archives of Disease in Childhood. Vol ; 74(2): 129–131. [PubMed: 8777661]

[12] Barr.R.G; antel .M.S;Young. S.N; Wright .J.H; Hendricks. L.A; Gravel. R., (2000), The response of crying newborns to sucrose: Is it a "sweetness" effect? Physiology & Behavior.; Vol 66(3): 409–417. [PubMed: 10357429]

[13] Fraga. C.G; Relevance, (2005), Essentiality and toxicity of trace elements in human health. Mol Aspects Med. Vol ;26: 235–244

[14] Osredkar.J; ustar .N,(2011), Copper and Zinc, Biological Role and Significance of Copper/Zinc Imbalance. J Clinic Toxicol,Vol :3: 1 – 18.

[15] Takeda. A, (2011), Zinc Signaling in the Hippocampus and Its Relation to Pathogenesis of Depression. Mol Neurobiol. Vol ;44(2):166-174

[16] Qiu. J; Zhang .C; Borgquist. A; Nestor. C.C;

Smith. A.W; Bosch. M.A; et al, (2014), Insulin excites, anorexigenic proopiomelanocortin neurons via activation of canonical transient receptor potential channels. Cell Metab.J, Vol ;19: 682–693. doi: 10.1016/j.cmet.2014.03.004

[17] Angelova .MG; Petkova-Marinova .TV; Pogorielov. MV;Loboda; et al ,(2014), Trace element status (iron, zinc, copper, chromium, cobalt, and nickel) in iron-deficiency anaemia of children under 3 years. Anemia.J . vol 2014: 1–8 . doi:10.1155/2014/ 718089

[18] Ho. E, (2004), Zinc deficiency, DNA damage and cancer risk, J. Nutr. Biochem.Vol ;15: 572–578.

[19] Livingstone .C, (2015), Zinc: Physiology, Deficiency, and Parenteral Nutrition, Nutr. Clin. Pract. J, Vol ;30(3): 371 – 382.

[20] Bonaventura.; Benedetti. G; Albarède. F;Miossec. P, (2014), Zinc and its role in immunity and inflammation. Autoimmun Rev. Autoimmun Rev. Vol ;14(4): 277-285. doi:10.1016/j.autrev.2014.11.008

[21] Wong .C.P; Rinaldi .N.A;Ho. E,(2015), Zinc deficiency enhanced inflammatory response by increasing immune cell activation and inducing IL6 promoter demethylation. Mol Nutr Food Res. NCBI .Vol 59(5): 991-999, doi:10.1002/mnfr.201400761

[22] Prasad.A.S. , (2013) ,Discovery of human zinc deficiency: its impact on human health and disease. Advance Nutr. j. Vol ;4: 176–190.

[23] Fowler .C.B; Pogozheva. I.D; LeVine .H; Mosberg. H.I,(2004), Refinement of a homology model of the mu-opioid receptor using distance constraints from intrinsic and engineered zinc-binding sites. Biochemistry.J, Vol ;43:8700–8710.

[24] Josko. O; Natasa .S , (2011), Copper and Zinc, Biological Role and significance of Copper/Zinc Imbalance , J Clinical Toxicol, vol 3: 1-8 doi.org/10.4172/2161-0494.S3-001

[25] Ciubotariu. D; Ghiciuc. C. M; Lupuşoru. C. E, (2015), Zinc involvement in opioid addiction and analgesia-should zinc supplementation be recommended for opioid-treated persons? Substance Abuse Treatment, Prevention, and Policy, Vol 10(1) : 175-185. doi:10.1186/s13011-015-0025-2.

[26] Araya .M; Pizarro. F; Olivares. M; Arredondo .M; Gonzalez M ; et al, (2006), Understanding copper homeostasis in humans and copper effects on health. Biol Res . Vol 39: 183-187

[27] Diana .CI; Cristina .M;Catalina .E, (2015), Zinc Imbalance and the Opportunity of Zinc supplementation in Alcoholic and Drug users, The Medical-Surgical Journal, Vol 119 (3):103-114

[28] Chan .K.W; Tan .G.H; Wong. R.C,(2013), Investigation of trace inorganic elements in street doses of heroin. Sci Justice. 2013;53:73–80. doi:10.1016/ j.scijus.2012.08.004.

[29] Rosse .R.B; Deutsch. L.H; Deutsch. S.I.,(2000), Medical assessment and laboratory testing in psychiatry. 7th ed. Textbook of Psychiatry. , Vol 1. Philadelphia, PA: Lippincott Williams &Wilkins; 2000:732-755.

[30] Karimollah ;Hajian-Tilaki ,(2013) , Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation , Caspian J Intern Med vol 4(2): 627-635

[31] United Nations Office on Drugs and Crime. World Drug Report 2015. http://www.unodc.org/wdr2015/. Accessed February 6, 2017.

[32] Yu, S.; Zhu, L., Shen; Q., Bai, X. & Di, X. ,(2015), Recent Advances in Methamphetamine Neurotoxicity Mechanisms and Its Molecular Pathophysiology. Behavioral Neurology, Vol 2015,1–11. DOI:10.1155/2015/103969

[33]Nwagha. U. I; Ikekpeazu. E. J; Ejezie. F. E; Neboh. E. E; Maduka. I. C, (2010),Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria. African health sciences,Vol 10(3): 248–52

[34]Mami. S; Eghbali. M; Cheraghi. J; Mami. F; Pourmahdi. B. M; Salati.A. P. ,(2011), Effect of opium addiction on some serum parameters in rabbit. Global Vet.Vol 7:310–314.

[35] Liu. I. M; Cheng. J. T, (2011), Mediation of endogenous β-endorphin in the plasma glucose-lowering action of herbal products observed in type1-like diabetic rats. Evid. Based Complement. Altern. Med. Article ID 987876, pp1-10. doi: 10.1093/ecam/nen078

[36] Azod. L; Rashidi. M; Afkhami-Ardekani. M; Kiani. G; Khoshkam. F, (2008), Effect of opium addiction on diabetes. Am. J. Drug Alcohol Abuse Vol 34: 383–388. doi: 10.1080/00952990802122580

[37]Sheldon. B. H; Quin, J. D,(2005), Diabetes and illicit drug use. Pract. Diabetes Int,Vol 22: 222–224. doi: 10.1002/pdi.821

[38] Sanli. D. B;Bilici. R;Suner. O; Citak. S; Kartkaya. K; Mutlu. F. S,(2015), Effect of different psychoactive substances on serum biochemical parameters. Int. J. High Risk Behav. Addict. Vol 4: 1–5.

[39]Falah S. Al-Fartusie; Saja N. Mohssan ,(2017) , Essential Trace Elements and Their Vital Roles in Human Body, Indian Journal of Advances in Chemical Science. Vol 5(3) : 127-136

[40] Grabrucker .A.M,(2014), A role for synaptic zinc in ProSAP/Shank PSD scaffold malformation in autism spectrum disorders. Dev Neurobiol. Vol 74:136– 146. doi:10.1002/dneu.22089.

[41] Hidalgo .J; Giralt .M; Garvey .JS; Armario. A,(1991), Effect of morphine administration on rat liver metallothionein and zinc metabolism, J .Pharmacol Exp Ther. Vol 259: 274–278.

[42] Tejwani GA; Hanissian. SH,(1990), Modulation of mu, delta and kappa opioid receptors in rat brain by metal ions and histidine. Neuropharmacology.J, Vol 29: 445–452.

[43] Sindreu .C; Storm .DR, (2011), Modulation of neuronal signal transduction and memory formation by synaptic zinc. Front Behav Neurosci. Vol ;5 : 68-70. doi:10.3389/fnbeh.2011.00068.

[44] Anna;Winiarska-ieczan;Edyta;Kowalczuk-Vasilev ;Katarzyna; et al,. (2019) , Dietary Intake and Content of Cu, Mn, Fe, and Zn in Selected Cereal Products Marketed in Poland. Biological Trace Element Research. Vol , 187 (2) : 568-578. DOI: 10.1007/s12011-018-1384-0

[45] Osredkar J ; Sustar N. ,(2011) Copper ; Zn , Biological Role and significance of copper/Zinc ImBalance , Journal of Clinical Toxicology2011, S:3 ;pp 3-9 . DOI: 10.4172/2161-0495.S3-001

[46]Volkow. N. D.;Wang. G. J.; Fowler. J. S; Telang. F, (2008), Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, Vol 363: 3191–3200.

[47]Katherine. A; VanBuskirk. B.A; Marc .N; Potenza, (2010) , The Treatment of Obesity and Its Co-Occurrence With Substance Use Disorders , J Addict vol 4: 1–10

[48]Duncan. A. E; Grant. J. D; Bucholz. K. K; Madden. P. A; Heath, A. C, (2009), Relationship between body mass index, alcohol use, and alcohol misuse in a young adult female twin sample. Journal of Studies on Alcohol and Drugs,Vol 70: 458– 466