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Trace Elemental Analysis and Some Mathematical Tools used to Study Migraine with the Help of Flame Atomic Absorption Spectroscopic Technique

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ABSTRACT

In the present work we have used some of the most clinically important and tested techniques of spectroscopy to the study of Migraine. We have evaluated trace elements such as Ca, Zn, Mg, Fe ,Cu, Na and K in the present work .The results of the study are very helpful to the clinicians and scientists to maintain the levels of different types of trace elements . On the basis of trace elemental analysis we are in a position to reduce the higher levels of the certain trace elements in a particular level of recommendations by the world health organization. We have also applied the statistical analysis to check the feasibility and suitability of the data with the application of theory of statistics. We have calculated multiple partial correlation coefficient in seven elements altogether in migraine patients and compared the data with the control persons. The multiple correlations such as $R_{Zn.CuMgCaFeNaK}$, $R_{Cu.MgCaFeNaKZn}$, $R_{Mg.CaFeNaKZnCu}$, $R_{Ca.FeNaKZnCuMg}$, $R_{Fe.NaKZnCuMgCa}$, $R_{Na.KZnCuMgCaFe}$, $R_{K.ZnCuMgCaFeNa}$ in migraine and control . The value of $R_{K.ZnCuMgCaFeNa}$ is found higher in the migraine patients in comparison to healthy persons .The other correlations were found to be lower in migraine patients .We must apply this study to maintain the levels of the trace elements according to correlation analysis .

Key word: Flame atomic absorption spectroscopy, trace elements, Migraine, Control, healthy

1 Introduction:

Allen, C.M.C.et.al.[1] have supplied variable information regarding neurological diseases and migraine is an enormous public health problem that has an impact on society, business, and families and most importantly on the individual sufferer. Migraine is a neurovascular brain disturbance. There are so many recurrent attacks of disabling headaches and associated symptoms found in the patients of migraine. These primary symptoms may be such as nausea, vomiting and sensitivity to light and sound. One of the

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main cause may be movement of head, which can trigger the migraine attack. Some of the patients sufferers complain of lack of sleepness, stress and odours. New studies show that the triggers all have something very common. It has been reported in the literature somewhere that the oxidative is linked between the triggers of migraine attack. The traditional migraine triggers all had a tendency to generate oxidative stress. The production of oxidative stress may produce an imbalance in the generation of free radicals and body' ability to detoxify or repair their damage. An acute migraine attack may be an attempt carried out by the human brain to protect itself. The leakage of certain chemicals in the brain of patient of migraine may heal the body automatically. Antioxidants could be used in thwarting triggers, which are preventing factors for migraine problem. A study was performed in New Castle University and reports were very informative regarding sea greens seaweed, which can be helpful in maintaining the level of migraine attack at minimum. Sea greens seaweed has a higher antioxidant capacity than fruit and vegetables. This antioxidant capacity is maintained throughout digestion. The higher concentration is released within the gut lumen and provides protection from oxidative damage.

May, A et.al.[2] have been reported that migraine is a neurovascular disorder characterized of neuronal aura symptoms and vascular headache. It has been reported in the literature before 1988 the migraine with aura is an idiopathic recurring disorder manifesting with attacks of neurological symptoms unequivocally localizable to cerebral cortex or brain stem, gradually developed over five to twenty minutes and lasting less than sixty minutes. Headache, nausea and or photophobia generally follow neurological aura symptoms directly or after a time interval of less than one hour. The headache generally ends within the period of four to seventy two hours. It may be completely absent.

Compbell,J.K.et.al.[3] have provided some of the most important disorders in the research. It has been already mentioned in the literature that headache is generally the primary complaint which brings a migrainur to consultant physician. Migraine can resemble to larger number of conditions presenting with headache.

Edlow,J.A.et.al.[4] have mentained that in acute cases of migraine, the migraine has to be distinguished from vascular headaches secondly to cerebrovascular diseases. Subarachnoid haemorrhage is the most important differential diagnosis entity. It has been already reported that contrary to subarachnoid haemorrhage migraine is a recurrent disorder.

Smetana,G.W.[5] has reported that adequate history and clinical examinations generally lead to error free diagnosis. The features most predictive of migraine, when compared to tension type-headache, are nausea, photophobia, phonophobia and exacerebation by physical activity.

Migraine is not just a bad headache. It is a collection of neurological symptoms which includes a severe recurring intense throbbing pain on one side of the head. It has been seen that one third of migraine attacks in which both sides of the head are attacked. Migraine is a syndrome. we may call it as a collection of symptoms, which arise from a common cause. The syndrome may occur in a complete form with all of the typical symptoms, in a less complete form, with some symptoms, or in specific groupings of symptoms. Migraine may be classified according to the grouping of its symptoms. The symptoms vary widely and migraine is generally misdiagnosed. Migraine is a moving target. The symptoms are very hard to evaluate

and may be changed from one attack to the next attack. It has been cited in the literature that many people fail to realize that migraine is a neurological disease, like epilepsy.

Migraine is also very common in children. It has been reported that this disease occur in children even at the age of eighteen months. A survey reported that about ten percent of school age children suffer from migraine. Half of all migraine sufferer have their first attack before the age of twelve years. Before the age of puberty, male children suffer from migraine more often than a female child. At the age of adolescence, the incidence increases more rapidly in female child than in boy. It is very difficult to diagnose migraine in children and adolescents. In childhood migraine, head pain is generally less dramatic or severe than other symptoms, such as unexplained nausea or vomiting. Abdominalpain or dizziness. It is not uncommon for attacks to occur with only minor or even no head pain. Motion sickness is an early warning of the predisposition to childhood migraine. It has been seen that after the adolescence, when estrogen influence begins in young girls, the risk of migraine and its severity rises in females. Estrogen adversely influences the brain receptors, which play a role in migraine development. More severe and more frequently attacks often result from fluctuations in estrogen levels. Menstrual migraine in women is very common through out the world and the severity is of higher order. The vast majority of these women also have migraine at other times of the month.

Livening, E.[6] and Sacks, O.[7] have studied migraine aura and found that it is exceptionally diverse. Russell,M.B.et.al.[8] have reported that migraine headache in the general population, the typical visual aura starts as a flickering, uncolored, zigzag line in the centre of the visual field and affects the central vision. It gradually progresses towards the periphery of the hemi field and often leaves a scotoma. The typical sensory aura is unilateral, starts in the hand, progress towards the arm and then affects the face and the tongue. The typical motor aura is half-side and affects the hand and arm. Russell,M.B.et.al.[9] have also studied the prevalence of migraine headache is normally moderate or severe and lasts the whole of the day of onset. Sometimes it happens two to three days. It is typically unilateral, pulsating and associated with nausea, photophobia and phonophobia.Physical activity makes it very worse and often the patient has to lie down during the attack. If the severity of the attack is very large the patient may vomit repeatedly. Rasmussem,B.K.et.al.[10] and Olesen,J.[11] have concluded that the usual notion is that the headache is identical in migraine with and without aura.

Sacks,O.[12] has studied the migraine attack are found that aura and headache are the hallmarks of migraine, the migraine attack can be seen an a broader sense. The author also described five stages in a typical migraine attack. These are (i) initial excitement, which is caused by a provocative stimulus, (ii) a state of engorgement, which is prodromal symptom, (iii) a state of prostration, which is attack itself with headache, (iv) a state of resolution, it occurs when attack ends either abruptly or slowly , and (v) a state of rebound, which is the state of well-being after attack.

Selby,G.[13] has putforward his thoughts and described migraine as a drama in three acts, the acts being premonitory symptoms, aura followed by headache and finally attack termination with a hangover. Blau, J.N.[14] has also give stress to the dynamic nature and different phases of migraine. Premonitory symptoms may occur hours to a day or two before a migraine attack (with aura or without aura). The generally consists of hyperactivity, hypo activity, depression, craving for special foods, repetitive yawing

and similar atypical symptoms. Typical hangover symptoms after the attack include physical and mental fatigue.

Welch, K.M.A.et.al.[15] and Welch, K.M.A [16] have given their valuable suggestions regarding this diseases and according to them the migraine has been considered as a state of neuronal hyperexcitability relating to both genetic and environmental factors. Ferrari, M.D[17] and Welch, K.M.A.[18] have also give their explanations for the migraine patient states and they believed that anyone can have migraine attack, but only migraineous are liable to recurrent attacks. There is an evidence that the brainstem with its wide connections is the heart of migraine.

Diener, H.E.et.al.[19] have been able to show activation of brainstem centers with positron emission tomography(PET) during migraine attack without aura. Diener, H.E.et.al.[19] and

Weiller,C.et.al.[20] have putforward their suggestions and according to them migraine generator is hypothesized to be located in these centers. The serotonergic nucleus raphe dorsalis(NRD) and noradrenergic locus coeruleus(LC) are anatomically very near these activation centers. The authors considered these as the brainstem centers of migraine.

These centers could play a role both in the onset of attacks and in their prolongation. Some of the authors [21-23] have given their valuable comments regarding these centers and suggested that these centres have extensive connections with the central nervous system, and when activated, are thought to lower the threshold for an attack.

Aurora, S.K. et.al.[24] and Wrag, S.H. [25] have reported that the occipital lobes, which is the generator of visual aura seem most vulnerable to this brainstem driven hypersensitivity. Parent, A. [26] and Goadsby, P.J. [27] have given a very useful explanation regarding the migraine generators such as NDR and LC which are defined by Weiller, C.et.al.[20] have well established connection with the hypothalamus which may account for premonitory symptoms such as yawning, craving for food and thrust before the main attack. Genetic factors such as gender form the basis underlying these hypersensitive brainstem pathways. Any factor inherited or acquired that affects the network at different time points can change the probability for attack onset with the one of the factors such as stress, emotional state, menstrual cycle, pregnancy, meditations and alcohol.

Welch, K.M.A.[18] has given the new thought according to him the stress is a common provoker of migraine, which can activate the brainstem via orbitofrontal cortex and set the attack in motion.

Leao, A.A.P. [28] and Leao, A.A.P. et.al.[29] have nicely described migraine aura. It is caused by a phenomenon similar to spreading depression. Lauritzan, M. et. al. [30] have given their thought related to the phenomenon and it was believed to occur also in humans, which is an innate feature of rodent brain. It could represent the expression of neuronal hyper excitability related to migraine. Some of the authors[31&32] applied the above theory and explanation was given by the authors was very fruitful and is described here if the human cortex is activated, a wave of neuronal excitation, followed by depression, start to spread along the cortex and manifests itself as migraine aura. Many not specific events and causes can put forward this phenomenon in motion and start an attack.

Welch, K.M.A.et.al.[15] and Wrag, S.H.[33] have supplied some informations related to occipital cortex according to them the occipital cortex is especially sensitive to spreading depression, which will be helpful in explaining why visual fortification spectra is the hallmark of migraine. Some of the authors [34-36] explained the neuronal phenomenon, which are followed by vascular changes and some of authors[37-39] studied and found that these vascular changes causing spreading origemia. Welch, K.M.A.[40] and Tietjen, G.E.[41] have modified their thoughts under some exceptional circumstances even ischemia, ischemia rarely to strokes.

May, A.et.al.[2] have also explained the migraine headache and reported that after the migraine attack is underway, the vascular headache of migraine generally supervenes. The part of the trigeminal nerve innervating cranial vasculature is at the heart of theory, which is very useful to explain the migraine headache. The trigeminovascular system when activated by spreading depression causes the blood vessels in the dura matter to dilate and neuropeptides to be released locally along the vessel. Moskowitz,M.A.et.al.[42] have studied thesepeptides and reported that they causes further vasodilation resulting in additional peptide release. This vicious circle keeps the headache going. Some of the authors [43&44] have studied neuropeptides and explained calcitonin-gene related peptide is one of the most important peptides has been the elevated levels in the jugular blood of migraine patients during the attack. Edvission,L.et.al.[45] clearly demonstrated that the elevation of the level of calcitonin-gene related peptide is likely cause of this trigeminus-driven neurogenic inflammation in the blood vessels of migraine patients. May,A.et.al.[2] have been also suggested that the trigeminopara sympathetic reflex is another vasodilating pathway thought to be central in migraine. The afferent limb of this arc is the trigeminal nerve, and the efferent limb the facial\greater superficial petrosal nerve of the parasympathetic nervous system. Moskowitz,M.A.[34] has studied aura and headache and found that the relationship between aura and how it leads to headache has been difficult to distinguished and explain the present theory is that spreading depression depolarises sensory nerve fibres of trigeminovascular system and sets up a painful sterile inflammatory state around the artery.

Sacks,O.[46] has given the explanation of autonomic nervous system and suggested that the autonomic nervous system is clearly involved in the migraine cascade with symptoms such as nausea and vomiting, among others. He has also seen that whole migraine attack as characterized by protracted parasympathetic tonus, preceded and followd by opposite sympathetic activation.

Welch,K.M.A.[18] has also given some importance to the sympathetic, noradrenergic arm of the autonomic nervous system. Havanka-Kanniaimen,H.[47] proposed that both sympathetic and parasyonpathetic disfunction are active in the mechanism of migraine. The complex nature of migraine attack and so many different types of symptoms, which are related to the autonomic nervous system make the study very difficult to interpret and firm conclusion regarding the patho-physiology of migraine related to the autonomic nervous system are still elusive.

Merikangas, K.P.[48] has studied the genetics of migraine with historical perspective and given a concrete analysis regarding the problem. Migraine tends to run in certain families and many studies have addressed the inheritance of migraine. It has been reported in the literature that there is no consensus on mode of

inheritance of common types of migraine, migraine with and without aura. Rasmussen, B.K. [49] has reported that migraine is so prevalent that it might occur in several family members just by chance.

Some of the authors [50-53] have studied and discussed migraine and reported that variable definition of migraine have been used so far andthere is no simple marker of migraine and the diagnostic criteria, which has some fluctuation time to time. Russell, M.B. et. al. [54] have given their suggestions and according to them the family studies are also demanding of some investigations that all members of individual family, which must be critically examined and interviewed, migraine with and without aura should be very precisely differentiated.

Haan, J. et. al. [55] have suggested that migraine is associated with many hereditary diseases and syndromes. The similarities with epilepsy are obvious. A genetic conclusion on the relationship cannot yet be drawn firmly. Davies, N.P. et. al. [56] have been pointed out that several epilepsy syndromes have been shown to be channellopathies. Sack, O. [57] has shown that suspected comorbidity of migraine with psychiatric and psychological problems is also well known. Merikang as, K.P. [58] and Merikang as, K.P. et. al. [59] have reported that the involvement of serotonin both in depression, anxiety and migraine is interesting also from genetic point view. Tietjen, G.F. [41] has suggested that there is a rare but clinically important association between migraine and stroke, especially young women. The pathophysiological mechanisms underlying this comorbility remain to be clarified.

Barbara, L.N. et. al. [60] have studies migraine and epilepsy and suggested that migraine and epilepsy are disorders that are very common, paroxysmal and chronic in many ways they are clearly different diseases. There are some pathophysiological overlaps and overlaps in clinical symptomatology, particularity with regard to visual and other sensory disturbances, pain and alterations of consciousness. Migraine affects about 12% of the general population and 2% of this population is of chronic migraine. The lifetime prevalence of epilepsy may be as high as 4% with the adult population having a prevalence of about 1%. Migralepsy was a first nomenclature given by William Lennox to describe a syndrome of migraine with aura where the migraine is immediately followed by an epileptic seizure in a way that provides an elevation to the suspicion that one triggered the other.

Sullivan-Mee,M et.al.[61] have studied migraine-related visual field loss with prolonged recovery. They have given findings on the cases of symptomatic visual loss. Ophthalmic, medical laboratory and imaging results did not identify and aetiology other than migraine as the cause of the vision loss. Their study represents a specific form of complicated migraine, Hemert, V.S, et.al [62] have studied migraine associated with gastrointestinal disorders and they have suggested that migraine may be associated with gastrointestinal disorders. The irritable bowl syndrome, inflammatory bowl syndrome and celiac disease are included in their studied. The patients who regular experienced gastrointestinal disorder symptoms have a higher prevalence of headache, with a stronger association with increasing headache frequency. Children with migraine are more likely to have experienced infantile colic compared to normal healthy children. Several studied demonstrated significant association between migraine and celiac disease, inflammatory bowl disease and irritable bowl syndrome.

Nacey,T.A.[63] has studied migraine and risk of stroke in young women. The author concluded that young women with migraine appear to be at higher risk of ischemic stroke than women without migraine. The risk is further increased by the co existence of other established risk including hypertension, smoking, and oral contraceptives.

Some of the author [2,64and65] have studied migraine headache pathophysiology and suggested that it leads to a chemical change in the dorsal raphe and locus ceruleus. The dorsal raphe has projections that terminate on cerebal arteries and after cerebral blood flow. Cranial vascular changes lead to activation of trigeminal afferents. The dura matter and large cerebral vessels, in the anterior and middle cranial fossae are primary innervated by branches of the ophthalmic division of the trigeminal and, in the posterior fossa, by the upper cervical dorsal roots, physical, chemical or psychological. Migraine is a neurovascular pain syndrome.The initial stimulus is form a trigger. Olesen,J, et.al [66]have studied Origin ofpain in migraine : evidence for peripheral sensitization and found that the Migraine is the most common neurological disorder, and the origin of painful impulses in the trigeminal nerve is still uncertain. Authors have suggested that migraine can be explained to patients as a disorder of the brain, and that the headache originates in the sensory fibres that convey pain signals from intracranial and extracranial blood vessels.

Muller,L.L. [67] has give some thought related to diagnose and management of migraine headache. He has also advised and given some information for the management of migraine and it is a dynamic process, because headaches inVol.ve overtime and medication tachy phylaxis may occur. It requires some change in therapy. Pathologic finding in the neck constitute an accepted aetiology or precipitant for headache. Osteopathic manipulative treatment may reduce pain input into the trigeminal nucleus caudalis, favorably altering neuromuscular-autonomic regulatory mechanism to reduce discomfort from headache.

Brenner, M.et.al.[68] have studied unusual headache syndromes in children and suggested that the most common headache syndromes diagnosed are migraine, tension type and chronic daily headache in children has focused on these clinical entities. The authors have successfully claimed that the article is helpful in providing an overview of some of more unusual headache syndrome in children and adolescents.

Annequin,D et.al.[69] have studied migraine and headache in childhood and found that the diagnosis of migraine is extensively underestimated and misdiagnosed in pediatric population. Due to adequate supply of some specific biologic marker, specific investigation or brain imaging generally reduce these clinical entities to a psychological illness. Authors have also suggested that daily prophylactic pharmacological treatments may be prescribed in second line of action after the failure of non-pharmacological treatment.

We would like to provide some more informations regarding migraine problem with special references to trace element analysis. If we maintain a proper mineral balance, this mineral balance included both micro minerals and macro minerals is good for health. It has seen that migraine sufferers tend to not only have mineral imbalance and deficiencies but also excess levels of different harmful elements inside their bodies. Such type of abnormalities can lead to hormone imbalances, neurotoxicity or excruciating head pain in the form of migraines. A human system needs just the proper and correct amount of the trace minerals to perform necessary functions such as nutrient metabolism and enzymatic breakdown, all of which are very critical in balancing homeostasis. If these level are very high in comparison to healthy

people, bodily tissue can become inflamed, which results in a host of chronic disease. If our body is deficient in a particular type of mineral. The metabolism will substitutive another type of mineral for that function. Such type of substitution leads to suppressed metabolism ,which may result in greater amounts of inflammation and greater fatigue, stress. We can say a greater risk of migraines.

Friedman, B.W.et.al. [70] have proposed that some macro minerals and trace elements have gained recognition as important for the treatment and diagnosis of migraine.

Dooma, O. et.al [71] have suggested that some minerals and trace elements have started to gain recognition as biological parameter in the pathogenesis of migraine. There is a small collection of literature available regarding the role of trace elements in various diseases. The trace element may play a vital role in the pathogenesis of diseases. Authors have also given some stress to their opinion that metals may have a role in the pathogenesis of acute migraine. The trace metals deserve more and more attention in the field due to the therapeutic values and diagnosis in the clinical trials. A relationship between migraine and heavy metals is available in literature but the availability is very rare.

Rao A.N. [72] has given some information of trace metal and reported that several metal ions such as sodium, potassium, magnesium, and calcium are essential to sustain biological life. There are at least six additional metals are essential for optimal growth, development and reproduction i.e. manganese, iron, cobalt, copper, zinc, and molybdenum. If we have an element, which is required in amounts smaller than 0.01 percent of the mass of the organism is called a trace element. The trace metals function play a role as a catalyst for enzymatic activity in human system. However, all essential trace metals become toxic when their concentration is in excess. This happens normally when the levels of elements exceed by 40-200 fold those required for accurate nutritional response. In addition to the metals essential for human life, our diet including the water we drink and the air we breathe may contain toxic metals like mercury, lead, cadmium, chromium, silver, selenium, aluminum, arsenic and barium. These metals can causes chronic or acute poisoning and should be eliminated as much as possible from the living environment.

The effects of trace metals on human health are complex as it is fascinating. The high concentrations may prove toxic and the depletion in the concentrations of the essential trace elements may cause so many metabolic instabilities due to enzyme dysfunction. Equally, industrial-based metallic contamination of the air, soil and water supplies can have a dramatic impact on human life. There is a toxic accumulation of these elements due to the intake of various drugs.

McCall, J.T.et.al.[73] have studied the trace elements response and reported that awareness of trace elements play a very important role, either beneficial or harmful, in human health has increased. There are so many metabolic disorders in human are accompanied by alternations in the concentration of one or more trace elements in some body fluids such as serum or plasma.

It has been reported in the literature that toxic metal are systematic poisons, which inhibit some biochemical enzyme functioning, resulting in fatigue and malfunctioning of the body. These toxic metals are non-essential elements and are known to accumulate in tissues and biological fluids, producing acute and chronic toxicity. Depression and suicidal thoughts seem to be a natural part of heavy metal poisoning. Mental depression has sudden onset and usually is not caused by anyone set of the circumstances. It

seems to arrive when everything is going on smooth way. The clinical doctors, after putting their depressed patients through so many tests, finally refer them to a psychiatrist, which only prologs their misery. This can make them feel guilty for the feeling they cannot control.

It has been reported in the literature that the proportion of beneVol. ent trace element such as magnesium, chromium, manganese, and zinc in our food is directly correlated to the mineral density of the soil that it comes from [74]. The aferemented farming draw these already scarce minerals from the soil before they can enrich the food with migraine headache-preventing properties. Consequently, even consuming what we think are nutrient-dense foods that can leave us with nutritional deficiencies, which are especially determined to growing children, the elderly, and people who are already sick. To prevent a migraine headache, chronic fatigue, and the host of other maladies that accompany a deficiency of trace minerals. Trace minerals have several applications in preventing the migraine headache, aiding muscle activation, synthesizing protein and many other vital processes. If sparsmic vasodilation an shirking of brain centred blood vessels occur than a person is said to be suffering from a migraine headache. As the blood vessels expand, they trigger pain receptors in the brain, causing a migraine headache pain and the resulting symptoms. More research is started to correlate this spontaneous vasodilation with an imbalance in trace minerals like magnesium.

Trace elements can also target and treat the symptoms of chronic fatigue syndrome, another condition is characterized by weakness and pain of muscles. Trace element of such as calcium and magnesium must be in sufficient amounts to help combat these symptoms.

Pizza, V. et.al [75] have studied food intolerance in migraine and their study showed a high incidence intolerance in migraineurs. The dietry factor, which supplied more significant results were tyramine, yeast, solanaceae, coffee and cocoa. Experts are still trying to understand how tyramine can trigger migraines. Authors have also explained that tyramine can cause never cells in human brain to release the chemical norepinephrine. This compound has higher levels of tyramine in our system. If this level goes beyond a certain limit changes in brain leads to headache. Tyramine are derivatives of amino acids called tyrosine. Some of the tyrosine residue in foods such as cheeses or meats will naturally converted by bacteria into tyramines. This same process also occur in human intestinal tract. If the digestion is very low that allows bacteria which may convert tyrosine into tyramine. Authors confirmed a strong relationship between food intolerance and migraine considering that tyramine, coffee and cocoa are very important migraine precipitating factors.

Alan,Z.et.al.[76] have studied plasma levels of neuroexcitatory amino acids in patients with migraine or tension headache and they have reported that the neuroexcitatory amino acid ,glutamic acid, glutamine, glycine, cysteic acid and homocysteic were higher in migraine patients while total thiols (Cysteine\Cystine) were lower.

Leira,R.et.al [77] have studied the diet and migraine and suggested that some foods in our diet may spark off migraine attack in susceptible individuals. Substances in food may be the cause of modifications in vascular tone and bring migraine on those, which are sensitive and prone. Some of the substances are tyramine, phenylalanine, phenolic flavonoids, caffine, alcohol and food additives such as sodium nitrate, monosodium glutamate, and aspartane. Authors have also represented that another recognized trigger

for migraine is hypoglycemia. Such types of food are chocolate, cheese, citrus fruits, bananas, nuts, cured meats, dairy products, cereals, beans, hot dogs, pizza, food additives, coffee, tea, cola drinks, alcoholic drinks such as red wine, beer or whisky distilled in copper stills, all may bring on a migraine attack.

D`Eufemia, P.et.al.[78] have studied erythrocyte and plasma levels of glutamate and aspartate in children affected by migraine and reported that lower plasma glutamate and aspirate levels and significantly erythrocyte/plasma concentrations ratios of the amino acids with respect to controls. Frythrocycle asparate concentrations were significantly elevated in migraine compared to health controls. Authors have also suggested that due to imbalance of the excitatory amino acid ternover in the pathogenesis of migraine in children.

Harrington,M.G. et.al. [79] have studied cerebrospinal fluid sodium increate in migraine and found that modestly elevated extracellular Na(+) in MH(+) may cause the neural changes that underline clinical features of migraine.

Özeral,E. et.al.[8] have studied of copper, zinc and manganese in nail and serum from patients with migraine and reported that concentration of manganese in nail and serum was significantly higher in migraine patients than those of control subjects. The concentration of zinc and copper in nail were increased group in migraine group compared to control group. Authors have also suggested that the antioxidant enzyme activities are not negatively affected form the changes.

Scientists of Analytical Research Laboratory [81] have reported in the literature that many headaches when chronic are due to nutritional and biochemical imbalances in the human system. They have also reported that nutritional causes for headaches are muscle tension, sinus congestion and infection, toxic metals, hypertension, allergies and food sensitivities and reaction during retracing. Tension headaches are those caused by muscle tension in the neck and back. The structural imbalance, poor posture, or stress can precipitate the tension headache, metabolic imbalances may also play an important role. Low tissue levels of calcium and magnesium are one cause of excessive muscles tension and muscle cramps. A strong correlation between certain mineral imbalance and the tendency for migraine headaches has been revealed by hair analysis. If the imbalance of metals is corrected, the headache goes down automically. High copper levels are the most common biochemical cause of migraine headache. Copper has a stimulating effect upon catecholamine production such as epinephrine, norepinephrine, dopamine and serotonin. These chemical messengers and a frequently cause of arterial spasms or in other way irritate delicate structures within the brain. The major cause of the imbalance of copper is weak adrenal glands. The gland stimulate the liver to produce ceruloplasmin, which is the major copper binding protein. Due to excess value of this binding protein in the human body the human system is not capable to absorb this element. It creates so many problems. This problem occurs to a great extent before the menstrual period, which may help at the time of month in women.

Low sodium levels are associated with low adrenal gland activity. Adrenal insufficiency is a common cause of allergies, which may produce migraine headache. A high sodium level is associated with water retention that in some people may cause pressure upon vessels of the brain. Iron deficiency is a frequent cause of migraine headaches. If the levels of iron are replenished the headache disappears immediately. The higher

concentration of iron levels is associated with headaches also lead toxicity is very common, which is associated with migraine headaches. Lead plays a very important role in the causation of migraine headache by interfering with Calcium, Iron, Zinc and Copper metabolism. The elevated levels of mercury are associated with migraine because one possible reason is that a high mercury level is normally indicates the elevation of copper levels. High cadmium level may be associated with migraine because cadmium displaces Zinc in many sites in the human system. A deficiency of Zinc frequently allows for an excessive build up of copper, which is notorious for causing migraine headaches. Zinc is used to maintain elasticity of arteries.

When the oxidation rate is enhanced through nutrition and when the organs are functioning properly with the help of nutrition diet and other means the severity of toxic headaches certainly vanish.

Monor, J.et.al. [82] have studied migraine is a food-allergic diseases. They have examined some patients with severe migraine and the patient were taking the food, which helped to provoke migraine attack. Authors supplied the sodium cromoglycate to the patients. Sodium cromoglycate exerted a protective effect. This can prevent a hypersensitive mechanism as well as the symptoms of migraine. No immune complexes were found in these patients. Authors have finally decreased that the food-allergic reaction is the one of the primary causes of migraine.

Perkin, J.E.et.al. [83] have studied the diet and migraine and tried to give a suitable relationship between food intake and migraine headache. Nutritional factors played a part in triggering migraine in individuals with a predisposition of this disorder. They have also pointed out that over concern about diet must be excluded, otherwise it becomes another stress factor.

Marcus, D.A. [84] studied managing headache during pregnancy and lactation. He had reported that headache pattern for both primary and secondary headaches are modified in women during pregnancy. Women who continue to suffer from migraine or other headaches during pregnancy need effective clinical care to include appropriate diagnostic studies, counseling about expectations during pregnancy and lactation and modification in therapeutic regimens to minimize risk to the fetus and nursing baby.

Bener, A. et.al. [85] have studied genetic and environmental factors associated with migraine in school children. They have reported that there was a strong relationship between migraine and examinations. The most common environmental exposure for migraine was found to be working on a computer. Loud noise and hot climatic circumstances were also helped in increasing the frequency of migraine attack.

Miziara, L.et.al. [86] have studied menstrual headache. They have reported that most part of the headaches began two days before the first day of menstrual flow. Nausea and vomiting were the most frequent associated symptoms. The headaches had strong intensity in the first day of pain and reduced gradually until the last day of pain.

Hayriye, G.et.al. [87] have studied the level of trace elements and heavy metal in patients with acute migraine headache and reported that the levels of Cu in patients of migraine were (4.63±0.42) µg/dl and controls were (8.90±0.73) µg/dl. The levels of Fe were estimated in patients (0.97±0.07) µg/dl and control were (0.48±0.06) µg/dl. The levels of Mg were reported in patients as (10.98±1.09) µg/dl and in normals were (34.51±1.99) µg/dl.The levels of Zn were calculated in migraine patients as (0.24±0.01) µg/dl while

in normals the levels were (5.77±0.71) µg/dl. Authors have also investigated the level of Co in migraine patients and measured as (0.83±0.08) µg/dl and (0.88±0.05) µg/dl in controls. The levels of Pb were also calculated in migraine patients as (1.48±0.48) µg/dl and in control the level of Pb were (0.70±0.07) µg/dl. Authors have also studied the levels of Mn in migraine patients as (2.30±0.21) µg/dl and (0.62±0.07) µg/dl in controls. They concluded that the trace elements level disturbances might predispose patients to migraine attack. Author also found significantly high level of Mn in migraine diseases compare to healthy controls. The Mn facilitates the function of different types of enzyme, and is essential for normal development and body function, Administration of an Mn was clearly indicate the reduction in migraine attack.

2 Methodologies used in the Present Work:

2.1 Basic Theory of Flame Atomic Absorption Spectroscopy

The phenomenon of atomic absorption was first observed in 1802. Walsh proposed the atomic absorption spectroscopy for the quantitative analysis of elements [88]. Skoog et al. [89] have supplied relevant information about this technique in detail. Atomic absorption analysis inVol.ves measuring the absorption of light by vaporized ground state atoms and relating the absorption to concentration. The incident beam of light is attenuated by atomic vapor absorption according to Beer's Law. The instrumental and chemical parameters of the system must be geared towards the production of neutral ground state atoms of the proposed element for study. The conversion of sample from its native state to the atomic state can be achieved by using a method called flame atomic absorption spectroscopy (AAS) or an electric furnace. The sample undergoes a number of pretreatment steps prior to analysis in the furnace.

The sample is dried by evaporating the solvent in the first step. The organic matrix is decomposed by heating the sample in the second step. The heating temperature may go upto 1000^{o}C. Ultimately the furnace is rapidly heated to a temperature around 2400^{o}C to produce vaporized neutral atoms with as many as possible in their electronic ground states.

The absorption spectrum of the gas phase atoms is extremely narrow of the order ≤ 10^{-2} nm. Thus the ligand source used for absorbance measurements must be of exactly the correct wavelength and of narrow line width for Beer's law to remain valid. The light source used in AAS is a hollow cathode lamp in which light is emitted from excited atom of the same element which is to be determined. This means that the radiant energy corresponds directly to the wavelength, which is absorbable by atomized sample. This method gives up both sensitivity and selectivity. Other elements in the sample will not generally absorb chosen wavelength and thus, will not interfere with the measurement. Molecular species may also be formed during the step of atomization. This can alter the spectral characteristics of the analytes metal or can cause spectral interference at the wavelength being monitored. To reduce background interference, the wavelength of interest is isolated by a monochromator placed between the sample and the detector. Zeeman or D_2 techniques for background correction may also be used for complex matrices. We wish to use a graphite furnace atomic absorption spectrophotometer. The ashing an atomization processes can also be examined. We shall try to calibrate this instrument for different elements using a series of standard solutions.

AAS determines the presence of metal in liquid samples. It is an instrument to measure the concentration of metals in the sample. Metals will absorb ultraviolet light in their elemental form when they are excited by heat. Each metal has a characteristic wavelength that will be absorbed. This spectrophotometer locks for a particular metal by focusing a beam of ultraviolet light at a specific wavelength through a flame and into a detector. The sample of interest is aspirated into the flame. If the metal is present in the sample will absorb some of the light, which reduces the intensity. The instrument measures the change in intensity. The change in intensity may be converted into absorbance. If the concentration is made high, the absorbance will also rise.

It has been established in the literature that the AAS throw light and give informations regarding the number of gaseous metal atoms remain in the ground state normally. These ground state atoms are more capable of absorbing radiant energy of their own specific resonance wavelength. The light of resonance wavelength is passed through a flame containing the atoms, then some part of the light will be absorbed. The extend of absorption is proportional to the number of ground state atoms present in the flame. The atomic absorption spectroscopy is based on the same principle as the flame test used in qualitative analysis. In the flame, the ions are reduced to gaseous metal atoms.

$$\text{Compound} \xrightarrow{\text{heated}} \text{Atoms}$$

The high temperature of the flame excites a valence electron to a higher energy orbital. The atoms then emits energy in the form of visible light as the electron falls back into the lower energy orbital (ground state).

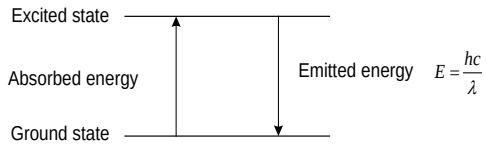

Figure 1: Energy diagram for the excited and emitted states

The ground state atom absorbs light of the same characteristic wavelengths as it emits when coming back from the excited state to the ground state. The intensity of the absorbed light is proportional to the concentration of the element in the flame. Absorbance or emission of atomic vapor can be measured.

2.2 Relationship between Absorbance and the Concentration of Atoms

Integrated absorption may be calculated by the formula, which is given below

$$\int k_\nu d\nu = \left(\pi e^2/mc\right) f\ N_{0\nu} \tag{1}$$

Here

K_ν is absorptioncoefficient at the frequency v
e is electronic charge
m is The mass of an electron
c is Velocity of light

f is the oscillatory strength of the absorbing line

N_o is the number of metal atoms per milliliter able to absorb the radiation

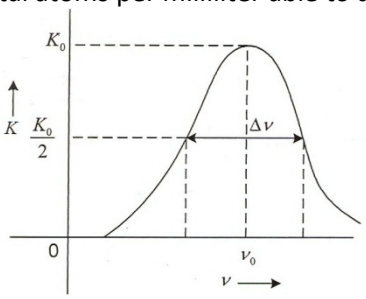

Figure 2: Graph between the absorption coefficient and frequency.

2.3 Effect of Temperature on Atomic Spectra

It has been established that the temperature changes number of atoms in ground and excited states . Boltzmann has established a simple relation for the number of atoms aS

$$\frac{N_1}{N_0} = \frac{P_1}{P_0} e^{-(\Delta E/KT)} \tag{2}$$

Here

N_1 are the number of atoms in excited state.

N_o are the number of atoms in the ground state.

K is Boltzmann constant equal to the value (1.28×10^{-23} j/k)

T is temperature

ΔE is the difference in energy between ground state and excited states.

P_1 are the number of states having equal energy at energy interval E_1

P_o are the number of states having equal energy at energy interval E_o

Detection Limit: The detection limit is the lowest concentration of an analyte that can be distinguished with reasonable confidence from a field blank

$$D = C \times 3\sigma / A \tag{3}$$

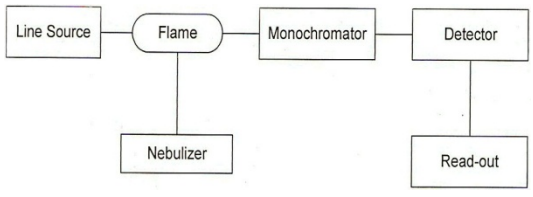

Figure 3 : Block diagram of a flame spectrophotometer

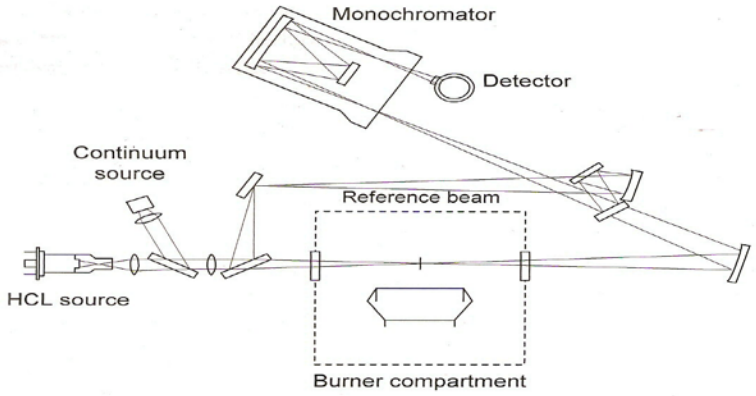

Figure 4 : Optical arrangement of atomic absorption spectrophotometer.

2.4 Mathematical and Statistical Formulation used in the Present Work

We would like to add here that simple formulae of statistics and mathematics have been used in the present work. We used different types of mathematical and statistical software for multiple and partial correlation coefficients in the study. We have calculated all multiple correlations with the help of determinant theory only.

Yule's Notation : If we consider a distribution involving 'n' random variables X_1, X_2 , X_3 ,....., X_n .Then the equation of the plane of regression of X_1 on X_2,X_3,.....,X_n is given by

$$X_1 = b_{12.34\ldots n}X_2 + b_{13.24\ldots n}X_3 + \ldots\ldots + b_{1n.23\ldots.(n-1)}X_n \tag{4}$$

The constants b' in Equation (1) are determined by the principle of least squares , i.e. ,by minimizing the sum of the squares of the residuals ,viz.,

The sum of the squares of residuals is given by

$$S = \sum X^2_{1.23\ldots\ldots n} = \sum\left[X_1 - b_{12.34\ldots n}X_2 + b_{13.24\ldots n}X_3 + \ldots\ldots + b_{1n.23\ldots.(n-1)}X_n\right]^2 \tag{5}$$

The summation being extended to the given values (N in number) of the variables.

Here we make N observations on each of the variables X_1 on X_2,X_3,....., X_n .

The normal equations for estimating $b_{12.34\ldots n}$ and $b_{13.24\ldots n}$

Using the principle of least squares, the normal equations for estimating the (n-1) ,b's are :

$$\frac{\partial S}{\partial b_{12.34\ldots n}} = 0 = -2\sum X_2\left(X_1 - b_{12.34\ldots n}X_2 + b_{13.24\ldots n}X_3 + \ldots\ldots + b_{1n.23\ldots.(n-1)}X_n\right) \tag{6}$$

$$\frac{\partial S}{\partial b_{13.24\ldots n}} = 0 = -2\sum X_3\left(X_1 - b_{12.34\ldots n}X_2 + b_{13.24\ldots n}X_3 + \ldots\ldots + b_{1n.23\ldots.(n-1)}X_n\right) \tag{7}$$

⋮ ⋮

$$\vdots \qquad\qquad \vdots$$

$$\frac{\partial S}{\partial b_{1n.23\ldots(n-1)}} = 0 = -2\sum X_n \left(X_1 - b_{12.34\ldots n} X_2 + b_{13.24\ldots n} X_3 + \ldots\ldots + b_{1n.23\ldots.(n-1)} X_n \right) \tag{8}$$

$$\text{i.e.,} \quad \sum X_i X_{1.23\ldots\ldots n} = 0, (i = 2, 3, \ldots\ldots, n) \tag{9}$$

which on simplification give

$$r_{12}\sigma_1\sigma_2 = b_{12.34\ldots n}\sigma_2^{\,2} + b_{13.24\ldots n} r_{23}\sigma_2\sigma_3 + \ldots\ldots\ldots\ldots\ldots + b_{1n.23\ldots.(n-1)} r_{2n}\sigma_2\sigma_n \tag{10}$$

$$r_{13}\sigma_1\sigma_3 = b_{12.34\ldots n} r_{23}\sigma_2\sigma_3 + b_{13.24\ldots n}\sigma_3^{\,2} + \ldots\ldots\ldots\ldots\ldots + b_{1n.23\ldots.(n-1)} r_{3n}\sigma_3\sigma_n \tag{11}$$

$$\vdots \qquad \vdots \qquad \vdots \qquad \vdots$$

$$\vdots \qquad \vdots \qquad \vdots \qquad \vdots$$

$$r_{1n}\sigma_1\sigma_n = b_{12.34\ldots n} r_{2n}\sigma_2\sigma_n + b_{13.24\ldots n} r_{3n}\sigma_3\sigma_n + \ldots\ldots\ldots\ldots\ldots + b_{1n.23\ldots.(n-1)}\sigma_n^{\,2} \tag{12}$$

Hence the eliminant of b's between Eqn.[1] , Eqn.[[7] , Eqn.[[8] and Eqn.[[9]is

$$\begin{vmatrix} X_1 & X_2 & X_3 & \ldots\ldots & X_n \\ r_{12}\sigma_1\sigma_2 & \sigma_2^{\,2} & r_{23}\sigma_2\sigma_3 & \ldots\ldots\ldots & r_{2n}\sigma_2\sigma_3 \\ r_{13}\sigma_1\sigma_3 & r_{23}\sigma_2\sigma_3 & \sigma_3^{\,2} & \ldots\ldots\ldots & r_{3n}\sigma_3\sigma_n \\ \vdots & \vdots & \vdots & & \vdots \\ r_{1n}\sigma_1\sigma_n & r_{2n}\sigma_1\sigma_n & r_{3n}\sigma_3\sigma_n & \ldots\ldots\ldots & \sigma_n^2 \end{vmatrix} = 0 \tag{13}$$

Dividing $C_1, C_1, C_1, \ldots\ldots\ldots, C_n$ by $\sigma_1, \sigma_2, \ldots\ldots\sigma_n$ respectively and $R_1, R_1, \ldots\ldots\ldots R_n$ by $\sigma_2, \sigma_3, \ldots\ldots\sigma_n$ respectively , we get

$$\begin{vmatrix} \frac{X_1}{\sigma_1} & \frac{X_2}{\sigma_2} & \frac{X_3}{\sigma_3} & \ldots\ldots & \frac{X_n}{\sigma_n} \\ r_{12} & 1 & r_{32} & \ldots. & r_{2n} \\ r_{13} & r_{23} & 1 & \ldots\ldots & r_{3n} \\ \vdots & \vdots & \vdots & & \vdots \\ r_{n1} & r_{n2} & r_{n3} & \ldots\ldots & 1 \end{vmatrix} = 0 \tag{14}$$

if we write

$$\omega = \begin{vmatrix} 1 & r_{12} & r_{13} & ..... & r_{1n} \\ r_{21} & 1 & r_{32} & .... & r_{2n} \\ r_{31} & r_{32} & 1 & ..... & r_{3n} \\ \vdots & \vdots & \vdots & & \vdots \\ r_{n1} & r_{n2} & r_{n3} & ..... & 1 \end{vmatrix} \tag{15}$$

and ω_{ij} is the cofactor of the element in the i[th] row and j[th] column of ω, we get from Eqn.[[11]

$$\frac{X_1}{\sigma_1}\omega_{11} + \frac{X_2}{\sigma_2}\omega_{12} + \frac{X_3}{\sigma_3}\omega_{13} + \frac{X_4}{\sigma_4}\omega_{14} + ... + \frac{X_n}{\sigma_n}\omega_{1n} = 0 \tag{16}$$

Equation [13] is the required equation of the plane of regression of X_1 on X_2, X_3 ....., X_n

Equation [11] can be written as :

$$X_1 = -\frac{\sigma_1}{\sigma_2}.\frac{\omega_{12}}{\omega_{11}}X_2 - \frac{\sigma_1}{\sigma_3}.\frac{\omega_{13}}{\omega_{11}}X_3 - ..... - \frac{\sigma_1}{\sigma_n}.\frac{\omega_{1n}}{\omega_{11}} \tag{17}$$

Comparing Eqn.[[13]with Eqn.[[1],we get

$$\left.\begin{aligned} b_{12.34....n} &= -\frac{\sigma_1}{\sigma_2}.\frac{\omega_{12}}{\omega_{11}} \\ b_{13.24....n} &= -\frac{\sigma_1}{\sigma_3}.\frac{\omega_{13}}{\omega_{11}} \\ &\vdots \\ b_{1n.23...(n-1)} &= -\frac{\sigma_1}{\sigma_n}.\frac{\omega_{1_n}}{\omega_{11}} \end{aligned}\right] \tag{18}$$

Variance of the residual

We consider here the plane of regression of X_1 on X_2,X_3,.....,X_n

$$X_1 = b_{12.34...n}X_2 + b_{13.24...n}X_3 + ... + b_{1n.23....(n-1)}X_n \tag{19}$$

Since all the X_i's are measured from their respective means ,we have

$E(X_i) = 0$; i =1,2,3,.....n $\Rightarrow$ $E(X_i).23.....n$

Hence the variance of the residual is given by :

$$\sigma^2_{1.23....n} = \frac{1}{n}\sum\left[X_{1.23....n} - E\left(X_{1.23....n}\right)\right]^2 = \frac{1}{n}\sum X^2{}_{1.23....n} \tag{20}$$

$$= \frac{1}{n}\sum X_{1.23....n} X_{1.23....n} = \frac{1}{n}\sum X_1 X_{1.23....n} \qquad \text{Using the property}$$

$$= \frac{1}{n}\sum X_1 \left[X_1 - b_{12.34.....n} X_2 - b_{13.24...n} X_3 - ..... - b_{1n.23...(n-1).} X_n \right] \tag{21}$$

$$= \sigma_1^2 - b_{12.34.....n} r_{12}\sigma_1\sigma_2 - b_{13.24...n} r_{13}\sigma_1\sigma_3 - ... - b_{1n.23...(n-1)} r_{1n}\sigma_1\sigma_n \tag{22}$$

$$\sigma_1^2 - \sigma_{1.23....n}^2 = b_{12.34.....n} r_{12}\sigma_1\sigma_2 + b_{13.24...n} r_{13}\sigma_1\sigma_3 + ... + b_{1n.23...(n-1)} r_{1n}\sigma_1\sigma_n \tag{23}$$

Eliminating the b's in equation Eqn.[[5] and the equations given below

$$r_{12}\sigma_1\sigma_2 = b_{12.34...n}\sigma_2^{\,2} + b_{13.24...n} r_{23}\sigma_2\sigma_3 + ... + b_{1n.23....(n-1)} r_{2n}\sigma_2\sigma_n \tag{24}$$

$$r_{13}\sigma_1\sigma_3 = b_{12.34...n} r_{23}\sigma_2\sigma_3 + b_{13.24...n}\sigma_3^{\,2} + ... + b_{1n.23....(n-1)} r_{3n}\sigma_3\sigma_n \tag{25}$$

$$\vdots \qquad \vdots \qquad \vdots \qquad \vdots$$

$$\vdots \qquad \vdots \qquad \vdots \qquad \vdots$$

$$r_{1n}\sigma_1\sigma_n = b_{12.34...n} r_{2n}\sigma_2\sigma_n + b_{13.24...n} r_{3n}\sigma_3\sigma_n + ... + b_{1n.23....(n-1)}\sigma_n^{\,2} \tag{26}$$

We get

$$\begin{vmatrix} \sigma_1^2 - \sigma_{1.23....n}^2 & r_{12}\sigma_1\sigma_2 & ..... & r_{1n}\sigma_1\sigma_n \\ r_{12}\sigma_1\sigma_2 & \sigma_2^2 & ..... & r_{2n}\sigma_2\sigma_n \\ \vdots & \vdots & \vdots & \vdots \\ r_{1n}\sigma_1\sigma_n & r_{2n}\sigma_2\sigma_n & ..... & \sigma_n^2 \end{vmatrix} = 0 \tag{27}$$

Dividing $R_1, R_2, ..., R_n$ by σ_1 , σ_2 ,....., σ_n respectively and also $C_1, C_2, C_3, ..., C_n$ by $\sigma_1, \sigma_2, \sigma_3, ..., \sigma_n$ respectively , we get

$$\begin{vmatrix} 1 - \frac{\sigma_{1.23...n}^2}{\sigma_1^2} & r_{12} & ..... & r_{1n} \\ r_{12} & 1 & ..... & r_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ r_{1n} & r_{2n} & ..... & 1 \end{vmatrix} = 0 \tag{28}$$

$$\Rightarrow \begin{vmatrix} 1-\frac{\sigma^2_{1.23\ldots n}}{\sigma_1^2} & r_{12} & \ldots\ldots & r_{1n} \\ r_{12}+0 & 1 & \ldots\ldots & r_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ r_{1n}+0 & r_{2n} & \ldots\ldots & 1 \end{vmatrix} = 0 \tag{29}$$

$$\Rightarrow \begin{vmatrix} 1 & r_1 & \ldots\ldots & r_{1n} \\ r_{12} & 1 & \ldots\ldots & r_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ r_{1n} & r_{2n} & \ldots\ldots & 1 \end{vmatrix} - \begin{vmatrix} 1-\frac{\sigma^2_{1.23\ldots n}}{\sigma_1^2} & r_{12} & \ldots\ldots & r_{1n} \\ 0 & 1 & \ldots\ldots & r_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ 0 & r_{2n} & \ldots\ldots & 1 \end{vmatrix} = 0 \tag{30}$$

$$\Rightarrow \quad \omega - \frac{\sigma^2_{1.23\ldots n}}{\sigma_1^2} = 0 \quad \Rightarrow \sigma^2_{1.23\ldots n} = \sigma_1^2 \frac{\omega}{\omega_{11}} \tag{31}$$

Coefficient of multiple correlation:

If we have a generalised case of multiple data then the multiple correlation coefficient of $X_1, X_2, X_3, \ldots\ldots, X_n$ is denoted by

$R_{1.23\ldots n}$ is the correlation coefficient between X_1 and $e_{1.23\ldots n} = X - X_{1.23\ldots\ldots n}$

So that

$$R_{1.23\ldots n} = \frac{Cov\left(X_1, e_{1.23\ldots n}\right)}{\sqrt{V\left(X_1\right)V\left(e_{1.23\ldots n}\right)}} \tag{32}$$

$$Cov\left(X_1, e_{1.23\ldots n}\right) = \frac{1}{N}\sum X_1 e_{1.23\ldots n} = \frac{1}{N}\sum X_1\left(X_1 - X_{1.23\ldots n}\right)$$

$$= \frac{1}{N}\sum X_1^2 - \frac{1}{N}\sum X_1 X_{1.23\ldots n}$$

$$= \frac{1}{N}\sum X_1^2 - \frac{1}{N}\sum X^2{}_{1.23\ldots n} = \sigma_1^2 - \sigma^2_{1.23\ldots n} \tag{33}$$

$$V\left(e_{1.23\ldots n}\right) = \frac{1}{N}\sum e^2{}_{1.23\ldots n} = \frac{1}{N}\sum X_1\left(X_1 - X_{1.23\ldots n}\right)^2$$

$$= \frac{1}{N}\sum\left(X_1^2 + X_{1.23\ldots n} - 2X_1 X_{1.23\ldots n}\right)$$

$$= \frac{1}{N}\sum X_1^2 + \frac{1}{N}X^2_{1.23\ldots\ldots n} - 2\frac{1}{N}\sum X_1 X_{1.23\ldots n}$$

$$= \frac{1}{N}\sum X_1^2 + \frac{1}{N} X_{1.23....n}^2 - 2\frac{1}{N}\sum X_{1.23..n}^2$$

$$= \sigma_1^2 - \sigma_{1.23....n}^2$$

$$R_{1.23...n} = \frac{\sigma_1^2 - \sigma_{1.23....n}^2}{\sqrt{\sigma_1^2\sigma_1^2 - \sigma_{1.23....n}^2}} = \frac{\left(\sigma_1^2\sigma_1^2 - \sigma_{1.23....n}^2\right)^{1/2}}{\sigma_1^2}$$

$$R_{1.23...n} = 1 - \frac{\sigma_{1.23...n}^2}{\sigma_1^2} = 1 - \frac{\omega}{\omega_{11}} \qquad (34)$$

We have used these statistical parameters for seven trace elements for the first time in the present work .We are able to show the effect of the trace elements altogether. We have also measured the correlation of the one fixed element and found the correlation with all six elements in the patients of migraine disease and compared the observed data with healthy persons in the present work . We have used the theory of 'Yule' for different types of correlations [90] .

3 Materials and Methods

Blood sample of Migraine patients along with normal healthy control were collected from the Department of Neurology, Safdarjang Hospital, New Delhi-110016 after the approval of ethical committee of the hospital. 10 ml freshly drawn blood from each patient was collected in clean and dry test tube without any anti-coagulant. The test tube was kept for 45 minutes at room temperature (22 ± 2°C) for the formation of clot. Sera of different patients were separated by centrifugation at 1500 r.p.m. upto 15 minutes and were collected in screw capped test tubes.

The atomic absorption spectral estimation of the serum samples from normal persons and Migraine patients were carried out on atomic absorption spectrophotometer Model No. AA- 6300 of Shimadzu Japan, at Deptt. of Environmental study University of Delhi 110007.

4 Results

We have measured the values of trace elements such as Cu, Fe, Zn, Na, K, Ca, Mg in Migraine patients and healthy normal control given in Table No.1. along with the latest availability of the literature.

Table 1. Compared Result along with work carried out by researchers on different mode of analysis us in different types of samples and diseases.

S. No.	Element	Type of sample	Mean + S.D.	Disease	Reference
1.	Calcium	Serum	(9.0 ± 0) mg/100 ml	Epileptic	John, H. et. al. [91]
2.	Calcium	Serum	(10.47 ± 1.16) µg/dl	Epileptic	Prasad, R. et. al. [92]
3.	Calcium	Serum	(10.76 ± 3.29) µg/dl	Controls	Prasad, R. et. al. [92]
4.	Calcium	Hair	(906 ± 796) µg/g	Controls	Lech, T. et. al. [93]
5.	Calcium	Hair	(520 ± 436) µg/g	Neurological disorders	Lech, T. et. al. [93]
6.	Calcium	Hair	(960 ± 419) µg/g	Controls	Avci et. al. [94]
7.	Calcium	Hair	(1162 ± 533) µg/g	Controls	Avci et. al. [94]

8.	Calcium	Hair	(947 ± 850) μg/g	Epileptic	Avci et. al. [94]
9.	Calcium	Hair	(1143 ± 437) μg/g	Epileptic	Avci et. al. [94]
10.	Calcium	CSF	(6.47 ± 0.87) μg/dl	Controls	Prasad, R. et. al. [92]
11.	Calcium	CSF	(5.85 ± 2.49) μg/dl	Epilepsy	Prasad, R. et. al. [92]
12.	Calcium	Serum	(2.46 ± 0.09) μg/dl	Controls	Barlow, P. J. et. al. [95]
13.	Calcium	Serum	(2.41 ± 0.08) μg/dl	Hyperactive children	Barlow, P. J. et. al. [95]
14.	Calcium	Hair	(430 ± 200) μg/g	Hyperactive children	Barlow, P. J. et. al. [95]
15.	Calcium	Hair	(694 ± 349) μg/g	Controls	Barlow, P. J. et. al. [95]
16.	Copper	Serum	(38.119 ± 2.68)μg/dl	Birth Asphyxia	Khanna R. S. et. al. [96]
17.	Copper	Serum	(29.677 ± 1.611)μg/dl	Controls	Khanna R. S. et. al. [96]
18.	Copper	Serum	(2.328 ± 0) mg/l	Smokers	Adnan, M. et. al. [97]
19.	Copper	Serum	(11.28 ± 0) μmol	Neurotoxic	Guidotti, T. L. et. al. [98]
20.	Copper	Serum	(112.9 ± 41.88)μg/dl	Epileptic	Prasad, R. et. al. [92]
21.	Copper	Serum	(66.46 ± 9.76)μg/dl	Controls	Prasad, R. et. al. [92]
22.	Copper	Serum	(111.22 ± 13.06) mg/l	Controls	Denitz, T. et. al. [99]
23.	Copper	Serum	(112.65 ± 9.33) mg/l	Controls	Denitz, T. et. al. [99]
24.	Copper	Serum	(114.55 ± 7.38) mg/l	Epileptic	Denitz, T. et. al. [98]
25.	Copper	Serum	(111.45 ± 5.97) mg/l	Epileptic	Denitz, T. et. al. [99]
26.	Copper	Serum	(0.86 ± 0.24) mg/l	Controls	Soylak, M. et. al. [100]
27.	Copper	Hair	(19 ± 7) μg/g	Controls	Avci et. al. [94]
28.	Copper	Hair	(16 ± 8) μg/g	Controls	Avci et. al. [94]
29.	Copper	Hair	(14 ± 9) μg/g	Epileptic	Avci et. al. [94]
30.	Copper	Hair	(10 ± 2) μg/g	Epileptic	Avci et. al. [94]
31.	Copper	Serum	(97.9 ± 0) μg/100ml	Controls	Delvis, H. T. et. al. [101]
32.	Copper	Serum	(102.2 ± 0) μg/100ml	Neurological disorders	Delvis, H. T. et. al. [101]
33.	Copper	Serum	(44 ± 24) mg/dl	Controls	Kumar, S. et. al. [102]
34.	Copper	Serum	(30 ± 17) mg/dl	GMF	Kumar, S. et. al. [102]
35.	Copper	Serum	(18 ± 3) mg/dl	Epilepsy	Smith and Bone [102]
36.	Copper	Serum	(18 ± 6) mg/dl	Controls	Smith and Bone [102]
37.	Copper	CSF	(43.34 ± 19.32) μg/dl	Controls	Prasad, R. et. al. [91]
38.	Copper	CSF	(36.69 ± 24.89) μg/dl	Epilepsy	Prasad, R. et. al. [91]
39.	Copper	Serum	(82.2 ± 16.64) μg/dl	Epilepsy	Kaji, H. et. al. [103]
40.	Copper	Serum	(97.3 ± 23.0) μg/dl	Controls	Kaji, H. et. al. [103]
41.	Copper	Hair	(38.2 ± 20.5) μg/g	Hyperactive children	Barlow, P. J. et. al. [94]
42.	Copper	Hair	(47.8 ± 31.7) μg/g	Controls	Barlow, P. J. et. al. [94]
43.	Iron	Serum	(108.636 ± 13.03)μg/dl	Birth Asphyxia	Khanna R. S. et. al. [95]
44.	Iron	Serum	(91.469 ± 2.42)μg/dl	Controls	Khanna R. S. et. al. [95]
45.	Iron	Hair	(9 ± 2) μg/g	Controls	Avci et. al. [93]
46.	Iron	Hair	(15 ± 9) μg/g	Controls	Avci et. al. [93]
47.	Iron	Hair	(6 ± 4) μg/g	Epileptic	Avci et. al. [93]
48.	Iron	Hair	(7 ± 5) μg/g	Epileptic	Avci et. al. [93]
49.	Iron	Serum	(386.0 ± 0) μg/100ml	Controls	Delves, H. T. et al. [100]
50.	Iron	Serum	(373.4 ± 0) μg/100ml	Neurological disorders	Delves, H. T. et al. [100]
51.	Iron	Serum	(20 ± 8) mg/dl	Controls	Kumar, S. et al.[101]
52.	Iron	Serum	(29 ± 15) mg/dl	GMF	Kumar, S. et al.[101]

53.	Iron	Hair	(8.8 ± 3.0) μg/g	Hyperactive children	Barlow, P. J. et al. [94]
54.	Iron	Hair	(15.7 ± 10.6) μg/g	Controls	Barlow, P. J. et al. [94]
55.	Magnesium	Serum	(0.87 ± 0.34) μg/dl	Epileptic	Prasad, R. et. al. [91]
56.	Magnesium	Serum	(0.93 ± 0.18) μg/dl	Controls	Prasad, R. et. al. [91]
57.	Magnesium	Serum	(24.13 ± 0.81) mg/l	Epileptic	Denitz, T. et. al. [98]
58.	Magnesium	Serum	(19.44 ± 0.53) mg/l	Epileptic	Denitz, T. et. al. [98]
59.	Magnesium	Serum	(24.33 ± 2.74) mg/l	Controls	Denitz, T. et. al. [98]
60.	Magnesium	Serum	(19.50 ± 0.64) mg/l	Controls	Denitz, T. et. al. [98]
61.	Magnesium	Hair	(40.5 ± 32.9) μg/g	Controls	Lech, T. et. al. [92]
62.	Magnesium	Hair	(29.3 ± 25.3) μg/g	Neurological disorders	Lech, T. et. al. [92]
63.	Magnesium	Hair	(259 ± 76) μg/g	Controls	Avci et. al. [93]
64.	Magnesium	Hair	(505 ± 219) μg/g	Controls	Avci et. al. [93]
65.	Magnesium	Hair	(329 ± 285) μg/g	Epileptic	Avci et. al. [93]
66.	Magnesium	Hair	(444 ± 203) μg/g	Epileptic	Avci et. al. [93]
67.	Magnesium	CSF	(1.31 ± 0.18) μg/dl	Controls	Prasad, R. et. al. [92]
68.	Magnesium	CSF	(1.03 ± 0.58) μg/dl	Epilepsy	Prasad, R. et. al. [92]
69.	Magnesium	Serum	(0.80 ± 0.04) μmol/l	Controls	Smith and Bone [103]
70.	Magnesium	Serum	(0.80 ± 0.06) μmol/l	Epilepsy	Smith and Bone [103]
71.	Magnesium	Hair	(53.9 ± 36.9) μg/g	Hyperactive children	Barlow, P. J. et. al. [95]
72.	Magnesium	Hair	(67.5 ± 47.4) μg/g	Controls	Barlow, P. J. et. al. [95]
73.	Zinc	Serum	(99.523 ± 7.44)μg/dl	Birth Asphyxia	Khanna R. S. et. al. [96]
74.	Zinc	Serum	(91.497 ± 2.44)μg/dl	Controls	Khanna R. S. et. al. [96]
75.	Zinc	Serum	(3.214 ± 0) mg/l	Smokers	Adnan, M. et. al. [97]
76.	Zinc	Serum	(8.20 ± 0) μmol	Neurotoxic	Guidotti, T. L. et. al. [98]
77.	Zinc	Serum	(64.82 ± 18.44)μg/dl	Epileptic	Prasad, R. et. al. [92]
78.	Zinc	Serum	(99.0 ± 8.0) mg/l	Controls	Denitz, T. et. al. [99]
79.	Zinc	Serum	(85.90 ± 2.79) mg/l	Controls	Denitz, T. et. al. [99]
80.	Zinc	Serum	(56.65 ± 4.62) mg/l	Epileptic	Denitz, T. et. al. [99]
81.	Zinc	Serum	(69.75 ± 3.07) mg/l	Epileptic	Denitz, T. et. al. [99]
82.	Zinc	Hair	(134.0 ± 9.41) μg/g	Controls	Denitz, T. et. al. [99]
83.	Zinc	Hair	(136.59 ± 8.56) μg/g	Controls	Denitz, T. et. al. [99]
84.	Zinc	Hair	(130.5 ± 7.9) μg/g	Epileptic	Denitz, T. et. al. [99]
85.	Zinc	Hair	(134.0 ± 7.1) μg/g	Epileptic	Denitz, T. et. al. [99]
86.	Zinc	Serum	(0.54 ± 0.21) mg/l	Controls	Soylak, M. et. al. [100]
87.	Zinc	Hair	(200 ± 61) μg/g	Controls	Avci et. al. [94]
88.	Zinc	Hair	(218 ± 87) μg/g	Controls	Avci et. al. [94]
89.	Zinc	Hair	(211 ± 63) μg/g	Epileptic	Avci et. al. [94]
90.	Zinc	Hair	(218 ± 127 μg/g	Epileptic	Avci et. al. [94]
91.	Zinc	Serum	(510 ± 0) μg/100ml	Controls	Delves, H. T. et. al. [101]
92.	Zinc	Serum	(617.9 ± 0) μg/100ml	Neurological disorders	Delves, H. T. et. al. [101]
93.	Zinc	Serum	(16 ± 9) mg/dl	GMF	Kumar, S. et. al. [102]
94.	Zinc	Serum	(13 ± 2) mg/dl	Epilepsy	Smith and Bone [103]
95.	Zinc	Serum	(14 ± 2) mg/dl	Controls	Smith and Bone [103]
96.	Zinc	CSF	(5.61 ± 2.02) μg/dl	Controls	Prasad, R. et. al. [92]
97.	Zinc	CSF	(6.64 ± 4.40) μg/dl	Epilepsy	Prasad, R. et. al. [92]
98.	Zinc	Serum	(83.2 ± 11.8) μg/dl	Hyperactive children	Barlow, P. J. et. al. [95]

99.	Zinc	Serum	(87.6 ± 12.4) μg/dl	Controls	Barlow, P. J. et. al. [95]
100.	Zinc	Hair	(97.5 ± 14.7) μg/g	Hyperactive children	Barlow, P. J. et. al. [95]
101.	Zinc	Hair	(123.0 ± 12.6) μg/g	Controls	Barlow, P. J. et. al. [95]
102.	Zinc	Serum	(1.6875 ± 1.8156) mg/l	Epilepsy	4.1.1.1.1.1 Kumar, S. *et.al.* [105]
103.	Zinc	Serum	(1.0267 ± 0.6347) mg/l	Control	Kumar,S. *et.al.* [105]
104.	Calcium	Serum	(4.0285 ± 1.0521) ml/l	Epilepsy	Kumar S. *et.al.* [105]
105.	Calcium	Serum	(0.0483 ± 0.0284) ml/l	Controls	Kumar,S. *et.al.* [105]
106.	Copper	Serum	(0.1767 ± 0.1087) mg/l	Epilepsy	Kumar,S. *et.al.* [105]
107.	Copper	Serum	(0.1329 ± 0.0380) mg/l	Control	Kumar,S. *et.al.* [105]
108.	Iron	Serum	(1.8483 ± 1.8079) mg/l	Epilepsy	Kumar,S. *et.al.* [105]
109.	Iron	Serum	(1.1826 ± 1.7671) mg/l	Control	Kumar,S. *et.al.* [105]
110.	Magnesium	Serum	(4.7017 ± 0.9548) mg/l	Epilepsy	Kumar,S. *et.al.* [105]
111.	Magnesium	Serum	(0.1098 ± 0.0310) mg/l	Control	Kumar,S. *et.al.* [105]
112.	Potassium	Serum	(0.1572 ± 0.0098) mg/l	Epilepsy	Kumar,S. *et.al.* [105]
113.	Potassium	Serum	(0.1443 ± 0.0043) mg/l	Control	Kumar,S. *et.al.* [105]
114.	Sodium	Serum	(3.2271 ± 0.0956) mg/l	Epilepsy	Kumar,S. *et.al.* [105]
115.	Sodium	Serum	(3.1203 ± 0.0708) mg/l	Control	Kumar,S. *et.al.* [105]

116	Zinc	Serum	(0.340 ± 0.1664) mg/l	AD	Kumar, S. et.al. [106]
117	Zinc	Serum	(1.0670 ± 0.6218) mg/l	Control	Kumar, S. *et.al.* [106]
118	Calcium	Serum	(3.1975 ± 0.7528) ml/l	AD	Kumar, S. *et.al.* [106]
119	Calcium	Serum	(4.8066 ± 1.0928) ml/l	Controls	Kumar, S. *et.al.* [106]
120	Copper	Serum	(0.7687 ± 1.2427) mg/l	AD	Kumar, S. *et.al.* [106]
121	Copper	Serum	(0.1402 ± 0.0430) mg/l	Control	Kumar, S. *et.al.* [106]
122	Iron	Serum	(6.9145 ± 3.0433) mg/l	AD	Kumar, S. *et.al.* [106]
123	Iron	Serum	(1.122 ± 1.6767) mg/l	Control	Kumar, S. *et.al.* [106]
124	Magnesium	Serum	(0.886 ± 0.3831) mg/l	AD	Kumar, S. *et.al.* [106]
125	Magnesium	Serum	(4.440 ± 1.6478) mg/l	Control	Kumar, S. *et.al.* [106]
126	Potassium	Serum	(0.1846 ± 0.319) mg/l	AD	Kumar, S. *et.al.* [106]
127	Potassium	Serum	(0.1385 ± 0.0083) mg/l	Control	Kumar, S. *et.al.* [106]
128	Sodium	Serum	(3.1768 ± 0.164) mg/l	AD	Kumar, S. *et.al.* [106]
129	Sodium	Serum	(3.1441 ± 0.0982) mg/l	Control	Kumar, S. *et.al.* [106]
130	Aluminum	Serum	(0.7082 ± 1.3450) mg/l	AD	Kumar, S. *et.al.* [106]
131	Aluminum	Serum	4.5880 ± 0.9235) mg/l	Control	Kumar, S. *et.al.* [106]
132	Zinc	Serum	(0.325 ± 0.155) mg/l	DMD	Kumar, S. *et.al.* [107]
133	Zinc	Serum	(1.072 ± 0.616) mg/l	Control	Kumar, S. *et.al.* [107]
134	Calcium	Serum	(0.154 ± 0.032) ml/l	DMD	Kumar, S. *et.al.* [107]
135	Calcium	Serum	(0.044 ± 0.027) ml/l	Controls	Kumar, S. *et.al.* [107]
136	Copper	Serum	(2.485 ± 1.668) mg/l	DMD	Kumar, S. *et.al.* [107]
137	Copper	Serum	(0.139 ± 0.042) mg/l	Control	Kumar, S. *et.al.* [107]
138	Iron	Serum	(11.086 ± 6.628) mg/l	DMD	Kumar, S. *et.al.* [107]

139	Iron	Serum	(1.122 ± 1.177) mg/l	Control	Kumar, S. *et.al.* [107]
140	Magnesium	Serum	(1.243 ± 0.371) mg/l	DMD	Kumar, S. *et.al.* [107]
141	Magnesium	Serum	(0.109 ± 0.0309) mg/l	Control	Kumar, S. *et.al.* [107]
142	Potassium	Serum	(0.2097 ± 0.0310) mg/l	DMD	Kumar, S. *et.al.* [107]
143	Potassium	Serum	(0.1371 ± 0.0068) mg/l	Control	Kumar, S. *et.al.* [107]
144	Sodium	Serum	(3.359 ± 0.242) mg/l	DMD	Kumar, S. *et.al.* [107]
145	Sodium	Serum	(3.1096 ± 0.0931) mg/l	Control	Kumar, S. *et.al.* [107]
146	Selenium	Serum	(0.1395 ± 0.0931) mg/l	DMD	Kumar, S. *et.al.* [107]
147	Selenium	Serum	(0.198 ± 0.119) mg/l	Control	Kumar, S. *et.al.* [107]
148	Cadmium	Serum	(0.36 ± 0.38) µg/dl	Migraine	Hayriye,G. et.al.[87]
149	Cadmium	Serum	(0.09 ± 0.14)µg/dl	Control	Hayriye G. et.al.[87]
150	Cobalt	Serum	(0.83 ± 0.08)µg/dl	Migraine	Hayriye G. et.al.[87]
151	Cobalt	Serum	(0.880.05 ±) µg/dl	Control	Hayriye G. et.al.[87]
152	Iron	Serum	(0.97 ± 0.07)µg/dl	Migraine	Hayriye G. et.al.[87]
153	Iron	Serum	(0.48 ± 0.06)µg/dl	Control	Hayriye G. et.al.[87]
154	Magnesium	Serum	(10.58 ± 1.09)µg/dl	Migraine	Hayriye G. et.al.[87]
155	Magnesium	Serum	(34.51 ± 1.99)µg/dl	Control	Hayriye G. et.al.[87]
156	Mangnese	Serum	(2.30 ± 0.21)µg/dl	Migraine	Hayriye G. et.al.[87]
157	Mangnese	Serum	(0.62 ± 0.07)µg/dl	Control	Hayriye G. et.al.[87]
158	Lead	Serum	(1.48 ± .048)µg/dl	Migraine	Hayriye G. et.al.[87]
159	Lead	Serum	(0.70 ± 0.07)µg/dl	Control	Hayriye G. et.al.[87]
160	Zinc	Serum	(0.24 ± 0.01)µg/dl	Migraine	Hayriye G. et.al.[87]
161	Zinc	Serum	(5.77 ± 0.71)µg/dl	Control	Hayriye G. et.al.[87]
162	Copper	Serum	(0.88 ± 0.05)µg/dl	Control	Hayriye G. et.al.[87]
163	Copper	Serum	(0. 83 ± 0.08)µg/dl	Migraine	Hayriye G. et.al.[87]
164	Zinc	Serum	(1.703 ± 1.841)mg/l	Migraine	Present work
165	Zinc	Serum	(1.0266 ± 0.63)mg/l	Control	Present work
166	Calcium	Serum	(2.776 ± 0.675)ml/l	Migraine	Present work
167	Calcium	Serum	(3.3866 ± 1.079)ml/l	Controls	Present work
168	Copper	Serum	(0.184 ± 0.11739)mg/l	Migraine	Present work
169	Copper	Serum	(0.132 ± 0.038)mg/l	Control	Present work
170	Iron	Serum	(1.548 ± 1.79)mg/l	Migraine	Present work
171	Iron	Serum	(1.182 ± 1.76)mg/l	Control	Present work
172	Magnesium	Serum	(0.63 ± 0.227)mg/l	Migraine	Present work
173	Magnesium	Serum	(0.6566 ± 0.120) mg/l	Control	Present work
174	Potassium	Serum	(4.139 ± 0.45)mg/l	Migraine	Present work
175	Potassium	Serum	(3.69 ± 0.1087)mg/l	Control	Present work
176	Sodium	Serum	(141.44 ± 3.13) mg/l	Migraine	Present work
177	Sodium	Serum	(135.86 ± 3.013)mg/l	Control	Present work

Determinant was formulated and used for calculation in case of healthy persons

$$\omega_{control} = \begin{vmatrix} 1 & 0.1817 & -0.3574 & -0.0733 & -0.4815 & -0.1028 & -0.076 \\ 0.1817 & 1 & 0.5037 & 0.6257 & 0.2237 & 0.2928 & -0.4297 \\ -0.3374 & 0.5037 & 1 & 0.0368 & 0.0997 & 0.2433 & 0.0325 \\ -0.0733 & 0.6257 & 0.368 & 1 & 0.3355 & 0.2623 & -0.3706 \\ -0.4815 & 0.2237 & 0.0997 & 0.3355 & 1 & -0.1591 & -0.353 \\ -0.1023 & 0.2928 & 0.2433 & 0.2623 & -0.1591 & 1 & 01699 \\ -0.076 & -0.4297 & 0.0325 & -0.3706 & -0.353 & 0.1699 & 1 \end{vmatrix} = 0.04362$$

Determinant was formulated and used for calculation in case of migraine patients

$$\omega_{migraine} = \begin{vmatrix} 1 & 0.5272 & -0.4207 & -0.0349 & -0.443 & -0.0518 & -0.0296 \\ 0.5272 & 1 & -0.5233 & 0.2428 & 0.4327 & 0.1453 & -0.0675 \\ -0.4207 & -0.5233 & 1 & 0.2981 & -0.2713 & -0.1938 & -0.2032 \\ -0.0349 & 0.2428 & 0.2981 & 1 & -0.2184 & 0.2784 & -0.2593 \\ -0.443 & 0.4327 & -0.2713 & -0.2184 & 1 & 0.0255 & -0.02 \\ -0.0518 & 0.1453 & -0.1938 & 0.2784 & 0.0255 & 1 & 0.5818 \\ -0.0296 & -0.0675 & -0.2032 & -0.2593 & -0.02 & 0.5818 & 1 \end{vmatrix} = 0.0795$$

Regression equations for seven elements are given in Table No.2 and Table No.3 for normal persons and migraine patients .

Table 2: Regression Equations for Seven Trace Elements for Normal Persons

S.N.	Regression Equations for Seven Trace Elements for Normal Persons
1	Zn = 17.6868458 Cu - 4.006586731 Mg - 2.686181857·10^{-1} Ca – 1.755239143·10^{-1} Fe - 4.273059652·10^{-2} Na + 5.668386721·10^{-1} K + 6.139472526
2	Cu= 1.943791627·10^{-1} Mg + 1.630552093·10^{-2} Ca + 4.767752251·10^{-3} Fe + 1.80533303·10^{-3} Na- 6.44509972·10^{-2} K + 3.180930383·10^{-2} Zn- 9.578515507·10^{-2}
3	Mg = -6.103388249·10^{-2} Ca - 1.777489228·10^{-2} Fe - 3.754961894·10^{-3} Na + 2.110589828·10^{-1} K - 1.339114367·10^{-1} Zn+ 3.612343601 Cu+ 2.734107721·10^{-1}
4	Ca = -5.472785084·10^{-2} Fe + 9.431354941·10^{-3} Na + 5.703050434·10^{-1} K - 9.447325736·10^{-1} Zn+ 31.88631863 Cu - 6.422459204Mg + 1.017734022
5	Fe = -1.767724672·10^{-1} Na - 1.217790474 K - 2.288478083 Zn + 34.56371115 Cu – 6.933848021 Mg - 0.202882869 x_6 + 32.69148313
6	Na= 8.512985018 K - 2.385506318 Zn +56.03961831 Cu -6.271970809 Mg+1.497070411·10^{-1} Ca - 7.569126732·10^{-1} Fe + 103.9595496
7	K = 3.736355861·10^{-2} Zn - 2.362188915 Cu + 0.416245432 Mg + 1.06886411·10^{-2} Ca - 6.156740816·10^{-3} Fe + 1.005145689·10^{-2} Na + 2.297548065

Table 3: Regression Equations for Seven Trace Elements for Migraine Patients

S.N.	Regression Equations for Seven Trace Elements for Migraine Patients
1	Zn = 17.6868458 Cu - 4.006586731 Mg - $2.686181857\cdot10^{-1}$ Ca – $1.755239143\cdot10^{-1}$ Fe - $4.273059652\cdot10^{-2}$ Na + $5.668386721\cdot10^{-1}$ K + 6.139472526
2	Cu= $1.943791627\cdot10^{-1}$ Mg +$1.630552093\cdot10^{-2}$ Ca +$4.767752251\cdot10^{-3}$ Fe +$1.80533303\cdot10^{-3}$ Na- $6.44509972\cdot10^{-2}$ K + $3.180930383\cdot10^{-2}$ Zn- $9.578515507\cdot10^{-2}$
3	Mg= $-6.103388249\cdot10^{-2}$ Ca -$1.777489228\cdot10^{-2}$ Fe -$3.754961894\cdot10^{-3}$ Na + $2.110589828\cdot10^{-1}$ K - $1.339114367\cdot10^{-1}$ Zn+ 3.612343601 Cu+ $2.734107721\cdot10^{-1}$
4	Ca = $-5.472785084\cdot10^{-2}$ Fe + $9.431354941\cdot10^{-3}$ Na + $5.703050434\cdot10^{-1}$ K – $9.447325736\cdot10^{-1}$ Zn+ 31.88631863 Cu - 6.422459204Mg + 1.017734022
5	Fe = $-1.767724672\cdot10^{-1}$ Na - 1.217790474 K - 2.288478083 Zn + 34.56371115 Cu - 6.933848021 Mg - 0.202882869 x_6 + 32.69148313
6	Na= 8.512985018 K - 2.385506318 Zn + 56.03961831 Cu - 6.271970809 Mg+ $1.497070411\cdot10^{-1}$ Ca - $7.569126732\cdot10^{-1}$ Fe + 103.9595496
7	K = $3.736355861\cdot10^{-2}$ Zn - 2.362188915 Cu + 0.416245432 Mg + $1.06886411\cdot10^{-2}$ Ca - $6.156740816\cdot10^{-3}$ Fe + $1.005145689\cdot10^{-2}$ Na + 2.297548065

We have also calculated Regression coefficients in the present work and given in Table No. 4.

Table 4. Regression Coefficients for Seven Elements in Migriane Patients and Control .

S.n.	Formula	Migraine	Control
1	$b_{ZnCu.MgCaFeNaK} = -\frac{\sigma_1}{\sigma_2}\times\frac{\omega_2}{\omega_{11}}$	-4.9500	-17.5353
2	$b_{ZnMg.CaFeNaKCu} = -\frac{\sigma_1}{\sigma_3}\times\frac{\omega_3}{\omega_{11}}$	-2.2462	-3.98736
3	$b_{Zn.CaCuMgFeNaK} = -\frac{\sigma_1}{\sigma_4}\times\frac{\omega_{14}}{\omega_{11}}$	-0.8072	2.6577
4	$b_{ZnFe.CuMgCaNaK} = -\frac{\sigma_1}{\sigma_5}\times\frac{\omega_{15}}{\omega_{11}}$	0.2439	-0.1739
5	$b_{ZnNa.CuMgCaFeK} = -\frac{\sigma_1}{\sigma_6}\times\frac{\omega_{16}}{\omega_{11}}$	-0.11495	0.4222
6	$b_{ZnK.CuMgCaFeNa} = -\frac{\sigma_1}{\sigma_7}\times\frac{\omega_{17}}{\omega_{11}}$	0.12793	-05690406

We have also calculated standard deviations for seven elements of control and migraine patients and are given in **TableNo.5**

Table5: Square of Standard Deviations for Migraine Patients and Control of Seven Elements

Square of Standard Deviations	Square of Standard Deviations In 'ω'	Migraine	Control
$\sigma^2 Zn.CuMgCaFeNaK$	$\sigma^2_{Zn}\frac{\omega}{\omega_{11}}$	5.226685×10^{-0}	1.0695×10^{-5}
$\sigma^2 Cu.MgCaFeNaKZn$	$\sigma^2_{Cu}\frac{\omega}{\omega_{22}}$	8.887×10^{-5}	2.69×10^{-5}
$\sigma^2 Mg.CaFeNaKZnCu$	$\sigma^2_{Mg}\frac{\omega}{\omega_{33}}$	2.3162×10^{-4}	1.762×10^{-4}
$\sigma^2 Ca.FeNaKZnCuMg$	$\sigma^2_{Ca}\frac{\omega}{\omega_{44}}$	8.35641×10^{-5}	1.106×10^{-6}
$\sigma^2 Fe.NaKZnCuMgCa$	$\sigma^2_{Fe}\frac{\omega}{\omega_{55}}$	1.97002×10^{-5}	6.8487×10^{-5}
$\sigma^2 Na.KZnCuMgCaFe$	$\sigma^2_{Na}\frac{\omega}{\omega_{66}}$	3.7253×10^{-0}	1.5529×10^{-4}
$\sigma^2 K.ZnCuMgCaFeNa$	$\sigma^2_{K}\frac{\omega}{\omega_{77}}$	9.469×10^{-5}	5.895×10^{-45}

We have calculated correlation coefficients between two elements for migraine patients and control persons and are given in TableNo.6. This table is the base of further calculations .

Table 6: Correlation Coefficients Between Two Elements for Migraine Patients and Control Persons.

S.N.	Correlation Coefficient	Value of the Correlation in Migraine	Value of the Correlation in Control
1	r_{ZnCu}	0.5272	0.1817
2	r_{ZnMg}	-0.4207	-0.3374
	r_{ZnCa}	-0.0349	-0.0733
4	r_{ZnFe}	0.443	-0.4815
5	r_{ZnNa}	0.0518	-0.1028
6	r_{ZnK}	-0.0296	-0.076
7	r_{CuZn}	0.5272	0.1817
8	r_{CuMg}	-0.5233	0.5037
9	r_{CuCa}	0.2428	0.6257

10	r_{CuFe}	0.4327	0.2237
11	r_{CuNa}	0.1453	0.2928
12	r_{CuK}	-0.0675	-0.4297
13	r_{MgZn}	-0.4207	-0.3374
14	r_{MgCu}	-0.5233	0.5037
15	r_{MgCa}	0.2981	0.0368
16	r_{MgFe}	-0.2713	-0.0997
17	r_{MgNa}	-0.1938	0.2433
18	r_{MgK}	-0.2032	0.0325
19	r_{CaZn}	-0.0349	-0.0733
20	r_{CaCu}	0.2428	0.6257
21	r_{CaMg}	0.298	0.0368
22	r_{CaFe}	-0.2184	0.3335
23	r_{CaNa}	0.2784	0.2623
24	r_{FeZn}	0.443	-0.4815
25	r_{FeCu}	0.4327	0.2237
26	r_{FeMg}	-0.2713	0.0997
27	r_{FeCa}	-0.2184	0.3335
28	r_{FeNa}	0.0255	-0.1591
29	r_{FeK}	-0.02	-0.353
30	r_{NaZn}	0.0518	-0.1028
31	r_{NaCu}	0.1453	0.2928
32	r_{NaMg}	-0.1938	0.2433
33	r_{NaCa}	0.2784	0.2623
34	r_{NaFe}	0.0255	-0.1591
35	r_{NaK}	0.5818	0.1699
36	r_{KZn}	-0.0296	-0.076
37	r_{KCu}	-0.0675	-0.4297
38	r_{KMg}	-0.2032	0.0325
39	r_{KCa}	-0.2593	-0.3706
40	r_{KFe}	-0.02	-0.353

41	r_{KNa}	0.5818	0.1699
42	r_{ZnZn}	1	1
43	r_{CuCu}	1	1
44	r_{MgMg}	1	1
45	r_{CaCa}	1	1
46	r_{FeFe}	1	1
47	r_{NaNa}	1	1
48	r_{KK}	1	1

We have also calculated the different types of cofactors for the making of a determinant form migraine patients and control persons and are given in **TableNo.7**

Table.7: Different Cofactors of the Correlations Migraine Patients and Control Persons

S.N.	PARAMETER	MIGRAINE	CONTROL
1	ω	0.0795	0.004362
2	ω_{11}	0.1222732	0.161866
3	ω_{22}	0.20931	-0.234366
4	ω_{33}	0.17764	0.3563
5	ω_{44}	0.38366	0.45910
6	ω_{55}	0.12959	0.19886
7	ω_{66}	0.20907	0.257872
8	ω_{77}	0.17700	0.08683
9	ω_{12}	0.03866	0.171519
10	ω_{13}	0.034086	0.122937
11	ω_{14}	0.01225	-0.07368
12	ω_{15}	-0.029155	0.07898
13	ω_{16}	-0.002400	-0.03287
14	ω_{17}	0.00384	-0.015790

We have finally calculated the multiple correlation coefficients for seven elements in migraine patients and control persons and are given in TableNo.8.

Table.8: Multiple Correlation Coefficients of Seven Trace Elements for Migraine Patients and Control Persons.

S.N.	PARAMETER	MIGRAINE	CONTROL
1	$R_{Zn.CuMgCaFeNaK}$	0.5935	0.8547033
2	$R_{Cu.MgCaFeNaKZn}$	0.7873	1.089115
3	$R_{Mg.CaFeNaKZnCu}$	0.7432	0.9367899
4	$R_{Ca.FeNaKZnCuMg}$	0.89038	0.951308
5	$R_{Fe.NaKZnCuMgCa}$	0.621712	0.8835
6	$R_{Na.KZnCuMgCaFe}$	0.7872385	0.9115077
7	$R_{K.ZnCuMgCaFeNa}$	0.7421	0.7087

We have also applied Student 't' test and Fisher 'z' test and measured the 'p' value and 't' value to test the level of significance of the data for seven trace elements and are given in Table No.9and Table no.10

Table.9: ' p' Value Table for Testing the Data At Level of Significance

S.N	Element	*P value*	*Two tailed or one tailed*	Significant or not significant at $p < 0.05$
1	Zn	0.15098	one tailed	not significant at $p < 0.05$
2	Cu	0.107407	one tailed	not significant at $p < 0.05$
3	Mg	0.374551	one tailed	not significant at $p < 0.05$
4	Ca	0.050301	one tailed	not significant at $p < 0.05$
5	Fe	0.486504	one tailed	not significant at $p < 0.05$
6	Na	0.000153	one tailed	significant at $p < 0.05$
7	K	0.004163	one tailed	significant at $p < 0.05$

Table 10 : 't' Value Table for Testing the Data At Level of Significance

S.N	Element	*t value*	*Two tailed or one tailed*	Significant or not significant at $p < 0.05$
1	Zn	0.1057046	one tailed	not significant at $p < 0.05$
2	Cu	1.277297	one tailed	not significant at $p < 0.05$
3	Mg	0.323862	one tailed	not significant at $p < 0.05$
4	Ca	1.713975	one tailed	not significant at $p < 0.05$
5	Fe	0.486504	one tailed	not significant at $p < 0.05$
6	Na	4.278335	one tailed	significant at $p < 0.05$
7	K	2.89825	one tailed	significant at $p < 0.05$

In the present work we have used technique of spectroscopy to the study Migraine. The results are very helpful to the clinicians and scientists to maintain the levels of different types of trace elements . On the basis of trace elemental analysis it may be helpful to reduce the higher levels of the certain trace elements in a particular level , which are recommendations by the world health organization. We have

also applied the statistical analysis to check the feasibility of the data with the application of theory of statistics. We have calculated multiple partial correlation coefficient in seven elements altogether in migraine patients and compared the data with the control persons. The multiple correlations such as $R_{Zn.CuMgCaFeNaK}$, $R_{Cu.MgCaFeNaKZn}$, $R_{Mg.CaFeNaKZnCu}$, $R_{Ca.FeNaKZnCuMg}$, $R_{Fe.NaKZnCuMgCa}$, $R_{Na.KZnCuMgCaFe}$, $R_{K.ZnCuMgCaFeNa}$ in migraine and control . The value of $R_{K.ZnCuMgCaFeNa}$ is found higher in the migraine patients in comparison to healthy persons .The other correlations were found to be lower in migraine patients .We must apply this study to maintain the levels of the trace elements according to correlation analysis .

5 Discussion

We have studied trace elements in the present work and try to throw some light on the possibilities of impact on human system . One of the major part of the work is still open for the clinicians to have good knowledge of the immunomodulatory aspects of trace elements. Immunomodulatory aspects of trace elements have also a great importance to study the effects on human system . It has been established that trace elements as essential micronutrients play an important role in different types of physiological processes . These are crucial for proper functioning of the immune system .The deficiency of the elements and infectious diseases are concomitantly observed and result in complex interactions normally . The trace elements such as selenium, zinc, copper, manganese, etc. depict the immunomodulatory effect and thus influence susceptibility to and the course and outcome of a variety of viral infections. Some trace elements inhibit viral replication in the host cells and therefore have antiviral activity. Many trace elements behaves like antioxidants. The trace elements are able not only to regulate the host immune response but also to alter the viral genome.

Studies suggest that macrominerals such as Na, Mg, K, Ca, Cl, and P—are found in very large quantities in biological tissues and are present in inorganic compounds. All form monatomic ions (Na^+, Mg^{2+}, K^+, Ca^{2+}, Cl^-) except for phosphorus, which is found as the phosphate ion (PO_4^{3-}). The body fluids of all multicellular organisms contain very high concentrations of these ions. Some ions (Na^+, Ca^{2+}, and Cl^-) are located primarily in extracellular fluids such as blood plasma, whereas K^+, Mg^{2+}, and phosphate are located primarily in intracellular fluids. Substantial amounts of energy are required to selectively transport these ions across cell membranes.

Maintaining optimum levels of macrominerals is important because temporary changes in their concentration within a cell affect biological functions. Nerve impulse transmission requires a sudden, reversible increase in the amount of Na^+ that flows into the nerve cell. Similarly, when hormones bind to a cell, they can cause Ca^{2+} ions to enter that cell

The important role of trace elements has been studied and found that and we may use it to transfer electrons in biological oxidation–reduction reactions. Iron and copper, for example, are found in proteins

and enzymes that participate in O_2transport, the reduction of O_2, the oxidation of organic molecules, and the conversion of atmospheric N_2 to NH_3.

It has been established that the trace elements also act as essential structural components of biological tissues or molecules. In many systems where trace elements do not change oxidation states or otherwise participate directly in biochemical reactions, it is often assumed, though frequently with no direct evidence, that the element stabilizes a particular three-dimensional structure of the biomolecule in which it is found . Some trace elements are essential nutrients for plant growth and often also for food and feed quality because the primary route for their intake by humans and animals is plants. These trace elements might better be called micronutrients. Included in this group are boron, chlorine, copper, iron, manganese, molybdenum and zinc. A problem with the term trace element is that it might suggest that, even if an element is not essential for plants or animals, it has no adverse effect on either. But some elements can accumulate even as traces to concentrations that are toxic to the plant or to the animal feeding on it. Several of the trace elements are essential for human as well as animal health. However, nutritionally important trace elements are deficient in soils in many regions of the world and the health problems associated with an excess, deficiency, or uneven distribution of these essential trace elements in soils are now a major public health issue in many developing countries. Therefore, the development of "foods and animal feeds" fortified with essential nutrients is now one of the most attractive research fields globally. In order to achieve this, knowledge of the traditional forms of agriculture, along with conservation, greater use of native bio-geo-diversity, and genetic diversity analysis of the cultivable crops, is a must.A number of trace elements serve as cofactors for various enzymes and in a variety of metabolic functions. Trace elements accumulated in medicinal plants have the healing power for numerous ailments and disorders.

Trace elements are implicated in healing function and neurochemical transmission (Zn on synaptic transmission);Cr and Mn can be correlated with therapeutic properties against diabetic and cardiovascular diseases. Certain transition group elements regulate hepatic synthesis of cholesterol

6 Conclusion

The developments in the field of trace elemental analysis are useful to the society and we are in a position to keep an eye to have safe life . The elements , which are very essential to the human system may be monitored and we can help the society . Sometimes the trace minerals are alarming elements and we have to maintain the levels properly with the consultation of some personalities like a clinical doctor and nutritionists may be very essential to help the society .Our study in the light of correlations between seven elements is very authentic and may be used to keep the levels under the limits of specifications .

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