Republic of Iraq

Ministry of Higher Education and Scientific Research

University of Babylon/College of Sciences

Department of Biology

The impact of Dopamine receptor D1 gene polymorphism in the criminal behavior of alcoholism

A Research

Submitted to the College of Science/University of Babylon In Partial Fulfillment of the Requirements for The Degree of Higher Diploma in science / Forensic Evidence

By

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2021 A.D **1443 A.H**

بسم الله الرحمن الرحيم

(وَلَقَدْ كَرَّمْنَا بَنِي آدَمَ وَحَمَلْنَاهُمْ فِي الْبَرِّ وَالْبَحْرِ وَرَزَقْنَاهُم مِّنَ الطَّيِّبَاتِ وَفَضَّلْنَاهُمْ عَلَىٰ كَثِيرٍ مِّمَّنْ خَلَقْنَا تَفْضِيلًا)

صدق الله العظيم

(الاسراء:٧٠)

DEDICATION

To the soul of my father and brother…

Allah forgive them and place them his haven .

My compassionate mother…

Who light up my way with her prayers. She was my refuge in crises and tribulations.

Dear sisters…

You were and still my support, lean and fame in all stages of life.

Dear wife and lovely kids…

My companions in my life.

Harith

ACKNOWLEDGEMENT

After the help of ALLAH for me in completing this study. 1 am thankful and grateful to his almighty.

I like to thank all those who helped me in completing this study in the best way. I'd start with my Supervisor Assit.Prof.Dr. Mona Najah Hassan Al-Terahi who was the best help for me by providing advice, guidance and evaluation along the preparation period of this research.

I am thankful to the Deanship of Science College, Babylon University for giving me the opportunity to get the requirements of this study. I especially thank Prof.Dr. Inas Muhammed Al-Rubaiee the dean of the college, and Prof.Dr. Uday Jassim Abdul Razzaq the head of the biology department and Assist.Prof.Dr. Wasan Mudher Abu-eltemmen.

I want to thank the members of teaching commission who taught me in High Diploma Stage they had given me the advanced concepts about the field of my study. Also, I want to thank all my friends for their support and help.

Finally, I will thank my family for support me and my friends in the hospital for their help.

Harith

Certificate:

I certify that this Research was prepared under my supervision at the department of Biotechnology, College of science, University of Babylon, as a partial requirement for the Degree of Higher Diploma of in Forensic Evidence.

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In view of available recommendation, I forward this thesis for debate by the Examination Committee.

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We, the examining committee, certify that we have read the thesis entitled (The impact of Dopamine receptor D1 gene polymorphism in the criminal behavior of alcoholism) and examined the student (Harith Fawzi Mourad Abed) in its contents and that our opinion it is accepted as a thesis for a degree of high diploma in forensic evidences with excellent degree.

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Summery

Drinking alcohol clearly has important effect on social behaviors, such as increasing aggression, self-disclosure, sexual adventuresomeness, and so on Alcoholism results from an interplay between genetic and environmental factors, and is linked to brain defects and associated cognitive, emotional, and behavioral impairment so the present study try to find connection between dopamine level and the aggressive behavior of alcohols drinker.

The study was conducted during the period from 20\6\2021 to 27\8\2021 on (40) alcoholism person's whom taken to the hospital to measure the level of alcohol in their blood by sending there samples to the forensic institution . and 30 healthy people as control (only men) with an average age (20-55 year) in Babylon city-Iraq.

When study the distribution of age categories compare between the alcohol drinker and control group it was found that less than 30 years was 55% at drink and 63.33 in control. more than 30 years was 45% at drink with compares with 36.66 controls . and the Body mass index were first less than 30 (40%) kg/m2 at drunk compare with (63.33) kg/m2 and more than 30 (17.5%) kg/m2 in alcoholism's in compare with (3.33) kg/m2 control group.

|It was found that duration of abuse of alcohol not give significant for the dopamine and alcohol level according to variable , less than 5 years , 5- 10 years and more than 10years.|

It was found that the percentage of drinking peoples in rural (17.5%) is less than urban (82.5%).

The present study revealed that the criminal behaviors were 60% violent, 17% normal drink, 12% paraphilia's, 8% drunk with possession of a drunk and 3% accident.

When studying dopamine levels for alcoholic drinkers, the study showed that concentration of dopamine in alcohols drinking peoples 4.29 ± 0.27 is less than

controls peoples 8.7 ± 0.22 and there was no significant difference between age , dopamine and alcohol concentration at heavy drinker table as well as in Body mass index

abuse drinking and criminal behaviors. The duration effect on dopamine concentration it's found that <5 years was 4.06±0.28550 and 5-10 years 5.1917±0.58367 and > 10 years was 1.9000±0.700 and it give significant in alcoholic drinking .

The genetic analysis of the VNTR, for the DAT1 VNTR gene showed three genotype (10 ,11 and deletion) among study groups, and the 10/11 repeat was more frequent in depression than control group.

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List of Abbreviations

bp	Base Pair
CODIS	Combined DNA Index System
DNA	Deoxyribonucleic Acid
EDTA	Ethylene Diamine Tetra Acetic Acid
PCR	Polymerase Chain Reaction
RFLP	Restriction Fragment Length Polymorphism
RNase	Ribonuclease
SNP	Single Nucleotide Polymorphism
STR	Short Tandem Repeats
TBE	Tris-Borate-Edta Buffer
VNTR	Variable Number Tandem Repeats
AD	Alcoholism dependence
TAAR	trace amine-associated receptors
AUD	alcohol use disorder
ADHD	a dopaminergic hyper function disorder
MATs	monoamine transporters

1: Introduction

Alcohol is a powerful chemical that can have a wide range of adverse effects on almost every part of the body, including brain, bones and heart and its associated risks can have both short-term and long-term effects (WHO,1987). Alcohol consumption, particularly heavier drinking, is an important risk factor for many health problems and, thus, is a major contributor to the global burden of disease. In fact, alcohol is a necessary underlying cause for more than 30 conditions and a contributing factor to many more. The most common disease categories that are entirely or partly caused by alcohol consumption include infectious diseases, cancer, diabetes, neuropsychiatric diseases (including alcohol use disorders), cardiovascular disease, liver and pancreas disease, and unintentional and intentional injury (Rehm,2011).

Alcohol is the cause of around 60 different medical conditions, and over 4% of diseases are directly related to alcohol consumption and the severity of alcoholism as a disease depends on a number of genetic, psychological and cultural factors. Social problems usually appear before physical health becomes impaired. Alcoholism is, broadly, any drinking of alcohol that results in significant mental or physical health problems (Littrell ,2014) and may lead to physical and psychological problems in persons of any age (Smith, 1995). Alcohol-induced changes in brain functions can lead to disordered cognitive functioning, disrupted emotions and behavioral changes. Moreover, these brain changes are important contributing factors to the development of alcohol use disorders, including acute intoxication, long-term misuse and dependence (WHO,2002).

Antisocial delinquency and criminal behavior is a serious social concern in most eastern and western societies (Reitz *et al*.,2005). The adverse effects of antisocial and criminal behavior involve individual life, family and wider society (Scott *et*

al.,2001). Criminal delinquency include disturbed family relations, substance use disorders, underachievement in educational and professional realms and continued involvement in violent criminal acts with resultant suffering of the victims of these criminal acts, their families and communities (Huesmann *et al*., 2009 ; Reef *et al*.,2011)

Some of the genetic and environmental antecedents of antisocial and criminal behavior have been identified (Moffitt *et al*.,2005). Shared environmental influences are also important factors governing criminal behavior (Lyons et al.,1995). The heritability of antisocial behavioral phenotypes, including criminal behavior and human noncriminal aggression, has been estimated to be approximately 50% (Vassos *et al*.,2014).

The dopaminergic system is involved in behavioral activation, motivated behavior, and reward processing (Everitt and Robbins, 2000). It also plays an active role in the modulation of aggressive behaviors.

In humans, the dopaminergic system has been linked to the recognition and experience of aggression. After administering a dopamine D2 receptor antagonist, sulpiride, subjects showed an impaired ability to recognize angry facial expressions (Lawrence *et al*., 2002). There is also evidence that impulsive behavior may be enhanced by elevated dopaminergic function (Brunner and Hen, 1997). Stimulants increase impulsivity in humans without the presence of an ADHD (Sostek *et al*., 1980). In addition,a dopaminergic hyper function disorder is associated with impulsivity and emotional dysregulation in patients with borderline personality disorders (Friedel, 2004). The mesolimbic dopamine system plays a crucial role in alcohol's reinforcing effects, as well as in the development and maintenance of alcohol use disorder (AUD) (Jayaram-Lindstrom *et al.*, 2016). Genes involved in dopaminergic neurotransmission, such as those expressing the dopamine transporter and dopamine-2 receptor, are promising candidate genes for

antisocial behaviors and traits (Guo *et al*.,2007; Ferguson *et al*.,2014). The polymorphisms in dopaminergic genes have been associated with psychiatric and developmental disorders like ADHD and autism, personality traits and substance use disorders. Moreover, the dopaminergic antagonists are pharmacotherapeutic employed for human aggressive behavior (de Almeida *et al*.,2005).

The aim of the study:

Study of the effect of alcohol on the level of dopamine and VNTR varation in D1 receptor and its relationship to criminal behavior in alcoholic drinkers

2: Literatures review

2.1: Alcoholism dependence (AD)

Alcoholism dependence (AD) is a complex behavioral and multifactorial disorder often associated with increased risk of developing other behavioral and psychiatric disorders such as anxiety, depression, anti social personality disorder and bipolar disorder, by affecting various neural mechanisms and part of brain with its effect according to the dose of consumption, genetic factors, etc. AD is a psychiatric disorder, with the life time population risk of approximately 5.4%.Family and twin's studies support the role of a genetic component in AD. It is widely accepted that the dopaminergic system play a crucial role in the development of psychoactive substance dependence including opiates, cocaine, nicotine and alcohol (Koob and Moal , 2001; Munafò *et al*., 2001; Lingford-Hughes and Nutt,2003).

The dopaminergic system regulates brain reward mechanism (Dick and Foroud,2003 ; Tupala and Tiihonen, 2004), so genes of reward pathway especially dopamine receptors are considered a strong candidate for alcohol dependence. Alcohol stimulates dopamine receptors, which release dopamine in the ventral striatum leading to increased alcohol consumption through mechanisms involving incentive salience attributions and craving (Kienast and Heinz,2006).Several psychiatric and neurological brain illnesses, including schizophrenia, depression, eating disorders, Parkinson's disease, and addiction, are linked to abnormal dopamine signaling (Glatt *et al*., 2003).

2.2: Alcohol chemical strictures

Alcohol, any of a class of organic compounds characterized by one or more hydroxyl (—OH) groups attached to a carbon atom of an alkyl group (hydrocarbon chain). Alcohols may be considered as organic derivatives

of water (H_2O) in which one of the hydrogen atoms has been replaced by an alkyl group, typically represented by R in organic structures. For example, in ethanol (or ethyl alcohol) the alkyl group is the ethyl group, —CH_2CH_3, the term alcohol originally referred to the primary alcohol ethanol (ethyl alcohol), which is used as a drug and is the main alcohol present in alcoholic drinks. (IUPAC,1997).

Ethanol is an interesting molecule. It is polar or hydrophilic (water-loving) due to the presence of the terminal hydroxyl group, so it dissolves in water. Yet because of the 2 carbon chain, it has a bit of non-polar character. There is no separation of electrical charges between the carbon atoms, thereby minimizing intermolecular interactions in aqueous solutions. Generally, carbon chains (saturated with hydrogen) give a molecule hydrophobic (water-fearing) character, making it less soluble in water. However, in the case of ethanol, the carbon chain is short enough so that the more polar -OH group dominates, giving the ethanol its polar character. In alcohols with relatively long carbon chains (4 or more), the polar effects of the -OH group are not sufficient to overcome the hydrophobic nature of the carbon chain, resulting in alcohols that are progressively less water-soluble (Isaac. 1975; IUPAC,1997).

Alcohols are polar, since they have oxygen-hydrogen bonds, which allow alcohol molecules to attract each other through hydrogen bonds. Since oxygen atoms are much more electronegative than hydrogen atoms, the oxygen-hydrogen bond is especially polar. The partially-negatively charged oxygen atom on one alcohol molecule is strongly attracted to the partially positively charged hydrogen atom on another alcohol molecule; this strong attraction results in much stronger intermolecular forces between alcohol molecules than there are between nonpolar alkanes of the same molar mass (Giorgio,2005). Alcohols are generally more soluble in water than alcohols of the same molecular mass; low-molecular weight alcohols such as methanol and ethanol are miscible with water, and solubility decreases as the number of carbons in the alcohol increases. Alcohols also have

much higher boiling points than alkanes of the same molecular weight: (Graham and Craig ,2000).

2.3: The Dopamine

The dopaminergic system plays important roles in neuromodulation, such as motor control, motivation, reward, cognitive function, maternal, and reproductive behaviors. Dopamine is a neurotransmitter, synthesized in both central nervous system and the periphery that exerts its actions upon binding to G protein-coupled receptors. Dopamine receptors are widely expressed in the body and function in both the peripheral and the central nervous systems. It has been described that an increase in dopamine release is prominent in the rewarding and positive reinforcing effects of drugs of abuse (Heinz *et al*. 2004, 2005).

Dopaminergic signaling pathways are crucial to the maintenance of physiological processes and an unbalanced activity may lead to dysfunctions that are related to neurodegenerative diseases (Marianne *et al*. 2019). The activated neurocircuits included dopaminergic projections, these findings initiated investigations of the dopaminergic reward system, which explored how dopamine-associated reinforcement establishes persisting habits (Birbaumer and Schmidt 2003). Intensive research in the past decades identified various neurotransmitter systems participating in the development and maintenance of increased and chronic alcohol intake in humans, e.g., dopaminergic (DA), serotonergic (5-HT), opioidergic and glutamatergic neurotransmission (Heinz *et al*. 2009). The mesocorticolimbic DA circuitry emerged to be of central importance, since alcohol and other drugs of abuse release DA in the striatum, which promote drug- seeking behavior, and consecutive intake. In comparison to primary or neutral reinforcers (like food, sleep, sex, or money), the effect of drugs on DA release does not appear to habituate (Di Chiara and Bassareo 2007). Presumably, this is caused by the drugs' pharmacological

activation of dopaminergic stimulation compared to primary rewards necessary for survival (Wise and Rompre 1989). It is, therefore, assumed that addictive drugs ‘‘hijack’’ the reward system, which preferentially responds to drug-associated reinforcement at the expense of non-drug reward (Gardner 2005).

In 2009, 9.5 million Germans consumed alcohol in a health-risking manner and 1.3 million subjects were considered to be alcohol-dependent (Drogenbeauftragte der Bundesregierung 2009). To address alcohol-specific processes, which contribute to the development of alcohol dependence, chronic alcohol effects on the human body and the brain need to be assessed and distinguished from effects associated with acute and intermittent alcohol use.

2.3.1: Dopamine as a Neurotransmitter

Extracellular dopamine levels are modulated by two main mechanisms: phasic and tonic transmission (Floresco *et al*. 2003). Phasic dopamine release is driven directly by action potentials in the dopamine-containing cells that result in fast and transient increase of dopamine concentrations near the presynaptic terminal. Conversely, tonic transmission occurs when dopamine is released, independently from presynaptic action potentials, and is regulated by the activity of other neurons and neuro-transmitter reuptake (Floresco *et al*. 2003). Tonic release generates milder and less spatially restricted increases in extracellular dopamine compared to phasic release (Venton *et al*. 2003). One interesting aspect of those firing mechanisms is related to the effect of DAT on dopamine extracellular levels. Phasic dopamine burst can reach apeak of 1.6mM saturating D2 receptors, while DAT activ-ity maintains dopamine extracellular levels by reuptake and the concentrations vary in a millisecond scale. In con-trast, the dopamine tonic transmission reaches a nanomolar concentration, varying in seconds to minutes scale, and is not disproportionately affected by DAT activity. Although the tonic concentration is lower, this is sufficient

to stimu-late presynaptic D2 receptors present on afferent terminals (Floresco *et al*. 2003; Grace *et al*. 2007). In most cases, dopamine release occurs through exocytosis led by changes in membrane potential (Liu *et al*. 2018). After dopamine enters the extracellular space, it can bind to postsynaptic receptors located on dendrites and soma or presynaptic autoreceptors (D2 and D3 receptors) located on the presynaptic neuron (Gardner 2000). After the postsynaptic neuron elicits an action potential, dopamine quickly becomes unbound (Floresco *et al*. 2003). Then, dopamine is taken back up by presynaptic cells, a process mediated by the dopamine transporter (DAT) or by monoamine transporters (MATs) (Miller *et al*. 1999).

Regarding its physiological role, dopamine cannot be simply classified as an excitatory or inhibitory neurotrans-mitter, since it can bind to different G protein-coupled receptors (GPCRs) and differentially modulate adenylate cyclase depending on the type of dopamine receptor involved (Beaulieu and Gainetdinov 2011). In general, activation of D1-like receptors leads to an increase in 3′-5′-cyclic adenosine monophosphate (cAMP) levels due to greater adenylyl cyclase activity (Vallone et al. 2000) Noteworthy, dopamine may act both as an inhibitory and excitatory neurotransmitter in presynap-tic neurons expressing D1-like receptors, depending on the downstream opening of potassium or sodium chan-nels. Therefore, the effects of dopamine depend on target cell receptors, second messenger responses, ion channelctivation in the postsynaptic plasma membrane, and pro-tein expression profiles (Beaulieu and Gainetdinov 2011).

Dopamine can also bind to trace amine-associated receptors (TAAR) (Borowsky *et al*. 2001), a family of intracellular receptors which modulate dopa-minergic activity in a manner not fully understood (Lindemann *et al*. 2008).

2.3.2: The dopamine system and brain reward circuitry

The dopamine (DA) system in the CNS includes the nigrostriatal pathway, the mesolimbic pathway and the tuberoinfundibular pathway. Dopamine is mainly produced in the substantia nigra, projected along the nigrostriatal pathways and stored in the striatum. Five subtypes of DA receptors have been identified and cloned. All of them function both individually and interactively as G-protein coupled receptors (Hui, and Gang, 2014).

There has been continuous research since the 1970s on the role DA plays in the brain reward system. The reward reinforcement circuitry is part of the limbic system that includes the ventral tegmental area (VTA), nucleus accumbens (NAc), ventral striatum, bed nucleus of the stria terminalis, hippocampus, amygdale, and other brain structures. DA is the main neurotransmitter of this system (Tupala and Tiihonen ,2004; Dichter *et al*.,2012). The reward system modulates primary physiological functions related to survival including the intake of food and water and sexual behavior. It is also the target of psychoactive substances including alcohol, cocaine, amphetamine and opioids. The mesolimbic DA pathway (the NAc is the central regulation structure for the reward effect) and the mesocortical pathway are the key structures that modulate the reward reinforcement circuitry (Tupala and Tiihonen ,2004; Charlet *et al*.,2013).

2.4: Influence of dopaminergic system to alcohol consumption

Several studies have confirmed a dose-response relationship between alcohol intake and DA release in the NAc (Yan,1999).Other experiments have also found that injection of ethanol in the NAc induces local DA release in a dose-response fashion (Yim,*et al*.,1998).

Several studies have shown that changes in the DA system in the CNS can influence drinking behaviors both in animals and in humans. Early animal models have shown that injection of the neurotoxin 6-hydroxydopamine (6-OHDA) in the ventricle or in

other brain regions destroys dopaminergic neurons. In 1975, Myers and Melchior found that CNS DA level decreased and rats showed a lower preference for alcohol after bilateral cerebral ventricle injection of 6-OHDA (Myers and Melchior.1975).

Alcohol, as a drug, like all the other drugs affects the central nervous system (CNS). The type of alcohol commonly consumed is ethanol with different alcoholic beverages containing different percentages of it. Ethanol acts to depress brain function, very much in the style of an anesthetic. Ethanol at low blood concentrations releases behaviours that are otherwise inhibited and usually produces feelings of relaxation and good mood which may facilitate socializing. Thus at low doses, ethanol is possibly useful. Caution however, needs to be exercised as even low quantities of alcohol affect the ability of hippocampus to process information, which in turn impairs memory formation. Higher doses of alcohol affect the brain further by inducing intoxication wherein the person may experience temporary loss of coordination and judgment (Gilpin and Koob, 2009).

During alcohol consumption, alcohol passes through the oesophagus into the stomach. There, about 20% of the consumed alcohol is absorbed by the gastric mucosa and delivered directly into the bloodstream. The remaining 80% enter blood circulation through the small intestine mucosa membrane. Through this particular pathway, ethanol (EtOH) is distributed throughout the human body within seconds and overcomes the blood–brain barrier due to EtOH liposoluble properties (Lindemann *et al*. 2008). In the brain, several neurotransmitter systems interact in a complex manner. It has been originally hypothesized by Wise (1982) that drug and alcohol-induced DA release mediates the hedonic feeling associated with druginduced reward (Di Chiara 2002).

Studies have shown that dopamine has a role in the incentive motivation associated with acute alcohol intoxication. This is so because alcohol consumption can be blocked by injecting low doses of a compound that interferes with dopamine's

normal activity (i.e., a dopamine antagonist) directly into the nucleus accumbens (Rassnick et al.,1992 ;Hodge *et al*.,1997) Furthermore, the consumption of alcohol and simply the anticipation of availability of alcohol results in production of dopamine in the nucleus accumbens, determined by the increased levels of dopamine in the fluid outside neurons(Weiss *et al*.,1993). However, lesions of the mesolimbic dopamine system do not completely abolish alcohol-reinforced behavior, indicating that dopamine is an important, but not essential, component of alcohol-reinforcement(Rassnick *et al*.,1993] Finally, alcohol withdrawal produces decreases in dopamine function in dependent individuals and this decreased dopamine function may contribute to withdrawal symptoms and alcohol relapse (Volkow *et al*,.2007).

Interaction of primary neurotransmitter systems involved in the acute initiation of alcohol intake. Inhibitory effects [via D2 receptors (DRD2) on the target cells (e.g., in the striatum) mediating GABAergic neurotransmission] are symbolized by dotted lines and excitatory effects [via D1 receptors (DRD1) on the target cells (e.g. in the striatum) mediating glutamatergic neurotransmission] by solid lines (modified according to (Heinz et al. 2009)). Abbreviations: DRD1 = dopamine D1 receptor; DRD2 = dopamine D2 receptor; GABA = gamma-aminobutyric acid K. Charlet *et al*. not been supported via pharmacological blockage of DA neurotransmission. The results of DA blockage studies in both animals and humans resulted in (motivational) apathy rather than anhedonia. Therefore, DA has been attributed a role in response-eliciting, but not in hedonic properties (‘‘wanting’’ instead of ‘‘liking’’) (Boileau *et al*. 2003; Di Chiara 2002; Heinz *et al*. 2009). Robinson and Berridge (1993) suggested that ‘‘liking’’ refers to the experience of pleasure, which is controlled by opioid and also potentially endocannabinoid and gamma-aminobutyric acid (GABA)-benzodiazepine neurotransmitter systems. Animal and human studies showed that alcohol stimulates endorphins, which act on mu-opiate receptors in the

NAc and also stimulate DA release in the same brain area via indirect effects on GABAergic neurons (de Waele *et al*. 1994; Ramchandani *et al*. 2010).

In detoxified alcohol-dependent patients, an increase of mu-opiate receptors can be found in the ventral striatum and medial prefrontal cortex (PFC), which was correlated to alcohol craving (Heinz *et al*. 2005a). The other component of reward, ‘‘wanting’’ or ‘‘craving’’, has been associated with the attribution of incentive salience to the drug of abuse and to drug-associated stimuli. Thus results in a type of incentive motivation that promotes direct approach toward reward-related stimuli and consumption of rewards and does not require elaborate cognitive expectations (Berridge *et al*. 2009). Wanting is assumed to be correlated with (phasic) cue-dependent DA release in the ventral striatum. Here, the work of Schultz et al. (1997) is of fundamental importance, which elucidated the role of DA neurons in mediating reward processing and reward-dependent learning.

The DA neurotransmitter system functions as a signalling network registering the occurrence of salient stimuli and the unexpected absence of reward, i.e., so-called prediction errors. However, DA in the NAc does not only code the salience, it also reflects the value of a potential reinforcer (Tobler *et al*. 2005). It has been suggested that reward-associated, stimulus-dependent DA release may be specifically vulnerable to sensitization, i.e., a stronger neuronal and behavioral response upon re-exposure to the pharmacological effects of repeated administration of dopaminergic. The Dopamine System in Mediating Alcohol Effects in Humans drugs (Heinz *et al*. 2004a). Altogether DA enhancing and endorphin-stimulating effects of acute alcohol intake can promote both the described hedonic response and a motivational response and may facilitate learning of motivational reactions to drugs and drug-associated stimuli. In drug-susceptible individuals, neural sensitization of incentive salience by drugs of abuse like alcohol may result in compulsive ‘‘wanting’’, which leads to consecutive drug intake. This can happen

regardless of whether or not the drugs are ‘‘liked’’, and thus contribute to the development of addiction (Berridge *et al*. 2009).

Nevertheless, DA involvement in incentive salience also affects processing of aversive stimuli. In the NAc, DA and glutamate interactions have been associated with fearful experiences common in both appetitive and fearful behaviors. That points to multiple functional modes of these substrates, depending on specific external and internal factors (Berridge *et al*. 2009). In humans, DA synthesis capacity in the amygdala was closely associated with processing of aversive stimuli (Kienast *et al*. 2008).

2.4.1: Acute Alcohol Effects on Emotion Regulation

Mood changes have been observed as a result of alcohol’s stimulating and depressant effects. In a fMRI-study by Gilman *et al*. (2008) observed that an increased response to fearful faces in the placebo condition (intravenous saline infusion) was abolished in the alcohol condition (intravenous alcohol infusion with a maximal BAC of 0.08%). Thus, alcohol may affect emotional processing in limbic and visual regions by decreasing the difference in activation between threatening and non-threatening stimuli, which can contribute to both the anxiolytic properties of alcohol and to risky decision making during intoxication. The authors also observed a substantial activation of the striatum across emotional conditions in the alcohol versus placebo condition. As Gilman *et al*. (2008) show, this increase in activation can be modulated by negative emotional stimuli: the participants exhibited decreased striatal activation when viewing fearful faces, a finding which suggests that threatening stimuli may have attenuated the reinforcing effects of alcohol in the striatum.

2.4.2: Acute Alcohol Effects on Personality

Acute alcohol intake can increase impulsive behavior (Dougherty *et al*. 2008; Marczinski *et al*. 2007). However, impulsiveness is a multi-faceted construct, The Dopamine System in Mediating Alcohol Effects in Humans which can occur in several domains including motor (inability to inhibit behavioral responses), cognitive (impulsive decision making) and non-planning (inability to maintain intentions and goals) (Barratt 1982). The inability to maintain inhibitory control over alcohol intake has been considered to be of fundamental importance for alcohol abuse (Fillmore and Weafer 2004).

Evidence indicates that the vulnerability to alcohol dependence may share a common genetic component with antisocial personality disorder, which may contribute to impulsive behavior and drug intake (Schuckit *et al*. 2004; Bowirrat and Oscar-Berman 2005). Cloninger (1987) suggested that Novelty Seeking (NS) is a partially heritable and DA-related personality trait, which is associated with DA neurotransmission, and that high NS and low Harm Avoidance (HA) predisposes an individual to an early onset of alcoholism (Cloninger 1987a). Volkow *et al*. (2006) hypothesised that low DRD2 availability is a partially heritable trait, which facilitates excessive alcohol and drug intake, while high DRD2 levels appear to be protective against alcoholism.

2.4.3: Long-Term Changes on Cognition/Emotion/Personality

The dopaminergic system regulates brain reward mechanism (Dick and Foroud,2003 Tupala and Tiihonen,2006), so genes of reward pathway especially dopamine receptors are considered a strong candidate for alcohol dependence. Alcohol stimulates dopamine receptors, which release dopamine in the ventral striatum leading to increased alcohol consumption through mechanisms involving incentive salience attributions and craving (Kienast and Heinz,2006). Aberrant

dopamine signaling is implicated in several psychiatric and neurological brain disorders such as schizophrenia, depression, eating disorders, Parkinson's disease and addiction (Glatt *et al*., 2003).

Reduced activity of central DA transmission may be an underlying cause of negative mood states such as anhedonia, depression and dysphoria in alcoholdependent patients (Heinz *et al*. 1994). These negative states can increase the risk of relapse in alcohol-dependent patients (Glenn and Parsons 1991). Contrary to this hypothesis, a study using Cloningers Tridimensional Personality Questionnaire (TPQ) (Cloninger 1987b) and neuroendocrinological challenge tests to assess DRD2 sensitivity showed that hyposensitivity of central DA receptors was not associated with anhedonia, depression or anxiety. Instead, relapsing patients even showed a trend toward lower anxiety and depression scores compared to abstinent patients. The same study indicated that harm avoidance (HA) is not a stable personality trait, but in fact decreased significantly in all patients during observation. Although Cloninger (Cloninger 1987a, b) assumed that novelty seeking (NS) is influenced by central DA transmission, and although reduced DA sensitivity predicted relapse in detoxified alcohol-dependent patients, NS was not correlated with the sensitivity of central DA receptors. Also, there was no significant difference between NS scores of subsequently abstinent and relapsing patients before or after detoxification. Instead, reduced sensitivity of central DA receptors in relapsing patients seemed to be a consequence of long-term alcohol consumption and mostly disappeared within the first eight days of abstinence. Therefore, DA sensitivity seems to have an effect of alcohol-consuming behavior, which modulates motivational states such as craving for alcohol (Heinz *et al*. 2005b) rather than negative mood (Heinz *et al*. 1996). Depression and anxiety, on the other hand, were correlated with 5-HT dysfunction in alcoholism (Heinz et al. 1998). In the domain of emotion perception, alcohol-dependent patients experience deficits in the processing of emotional facial

expressions (Frigerio et al. 2002; Kornreich *et al*. 2002; Uekermann and Daum 2008). An investigation of alcohol-dependent patients by Salloum *et al*. (2007) showed that patients displayed reduced functional activation while evaluating emotional facial expressions.

2.5: Gene variants related to DA systems and alcohol dependence

The dopaminergic system regulates brain reward mechanism (Dick and Foroud,2003 Tupala and Tiihonen,2006), so genes of reward pathway especially dopamine receptors are considered a strong candidate for alcohol dependence. Alcohol stimulates dopamine receptors, which release dopamine in the ventralstriatum leading to increased alcohol consumption through mechanisms involving incentive salience attributions and craving (Kienast and Heinz,2006). Aberrant dopamine signaling is implicated in several psychiatric and neurological brain disorders such as schizophrenia, depression, eating disorders, Parkinson's disease and addiction (Glatt *et al*., 2003).

The dopamine D2 receptor (*DRD2*) gene on chromosome 11 (q22-q23) has been found to be associated with increased alcohol consumption through mechanisms involving incentive salience attributions and craving in alcoholic patients (Pushplata *et al*.,2010). Alcohol, by stimulating dopamine receptors, promotes dopamine release in the ventral striatum leading to increased alcohol consumption through mechanisms involving incentive salience attributions and craving [Kienast and Heinz,2006]. Clinical investigation involving analysis of receptor density and function has implied that dopamine D2 receptor (DRD2) density and function being lower among alcoholics may be responsible for craving and subsequent relapse (Tupala and Tiihonen,2004) many studies have addressed possible association of DRD2 polymorphism with alcoholism. However, findings of these studies have largely remained controversial. Inconsistent results have been explained in terms of

DRD2 mediated "reward deficiency" syndrome, and/or population stratification bias (Blomqvist *et al*., 2000)

D1, D2 and D4 receptors and DA transporter polymorphisms have been shown to play a role in alcohol dependence, but there remains controversy about the pathways via which these effects are produced. In 1990 Blum and colleagues first proposed that: "the D2 receptor A1 allele is closely related to the development of alcohol dependence". They found that the D2 receptor A1 allele was associated with a 8.7 higher odds of developing alcoholism (Rice and Cragg, 2004). This finding has been replicated by many case-control studies and other work has shown that gene polymorphisms that inhibit the expression of the D2 receptor are associated with increased risk of alcohol dependence (Zhou *et al*.,2001; Melchior and Jones,2017). In support of this hypothesis, a recent study found increased alcohol intake among D2L receptor knock-out mice (Lahiri and Bevan,2020) . In contrast, other studies failed to find any association between the D2 receptor and alcohol dependence (Bamford *et al*.,2004; Wang *et al*.,2012). Possible reasons for these contradictory findings include differences in sample characteristics (e.g., types of alcohol dependence, selection of controls, and race/ethnicity) and other methodological differences across studies. Parallel work with D1 receptors by El-Ghundi and colleagues found lower alcohol preference and intake among D1 knockout mice compared to wild-type mice (Yin *et al*.,2006). Using a case-control design, Zhong and colleagues studied three genetic polymorphisms of D2 (TAQI A, TAQI B, -141CINS/DEL), the 48bp variable number tandem repeat (VNTR) of the 3rd exon of the D4 receptors, and the 40bp VNTR of the non-coding region at the end of the DA transporter gene 3' in a sample of Chinese Han individuals living in Yunnan province. They found that the D2 TaqIB genotype and allele frequencies were associated with alcohol dependence and that carriers of the B2 allele polymorphism

had a lower risk of alcohol dependence, but no differences were found for the other polymorphisms between cases and controls (Threlfell *et al*.,2012) .

3. Materials and Methods

3.1 Materials

3.1.1: Chemicals

Chemicals that used during this study are shown in table (3-1).

Table (3-1): Chemical substances and its origin

No.	Chemical	Company
1	Agarose	Bio Basic/Canada
2	D2000 DNA ladder	Biosharp/Korea
3	DNA Extraction kit	Geneaid/Korea
4	Ethanol	Biosolve company/USA
5	Ethidium bromide	Promega/USA
6	Loading dye 6X	Promega/USA
7	PCR Master Mix Kit	Promega/USA
8	TBE B. 10X	Bio Basic
9	Human Dopamine ELISA Kit	Bioassay technology/China
10	Proteinase K	Biolabs/England
11	***DAT1 VNTR* Polymorphism (primer)** (483pb) ***F:5'- TGTGGTGTAGGGAACGGCCTGA-3'*** ***R: 5'CTTCCTGGAGGTCACGGCTCAAGG3'***	Promega/USA (Glavina Jelaš et al.,2018)

3.1.2: Devices and Instruments

Table (3-2): Instruments and devices with its Supplying Company

No.	Devices and Instruments	Company
1	Autoclave	Haramaya/Japan
2	Centrifuge; Cooling Centrifuge	Hettich/Germany
3	Deep Freeze	GFL/Germany
4	Balance	Precisa/UK
5	Electronic Sensitive Balance	Denevr Instrument
6	Photo Digital Camera	Sony/Japan
7	Distillater	GFL/Germany
8	Elisa reader and washer	Biotek/USA
9	Micropipette	BIOZEK
10	Gel electrophoresis unite	Cleaver scientific/Japan
11	Photo documentation	Velber/France
12	Vortex mixer	Bioneer/Korea
13	Refrigerator	L.G
14	Thermo cycler	Cleaver Scientific
15	Water bath	Memmert
16	Disposable syringes	Homecare
17	Electrophoresis power supply	Cleaver Scientific
18	Gloves	Bio-touch
19	Eppendorf vial	Bio-touch
20	EDTA vial s	Bio-touch
21	Plastic cups	Bio-touch
22	Gel tube	Afco USA
23	Pipette tips	Applied Bio system USA

3.2: Study Design

The duration of sampling in this study was done during the period from 20\6\2021 to 27\8\2021 on (40) alcoholism person's whom taken to the hospital to measure the level of alcohol in their blood and 30 healthy people as control. Sample collection

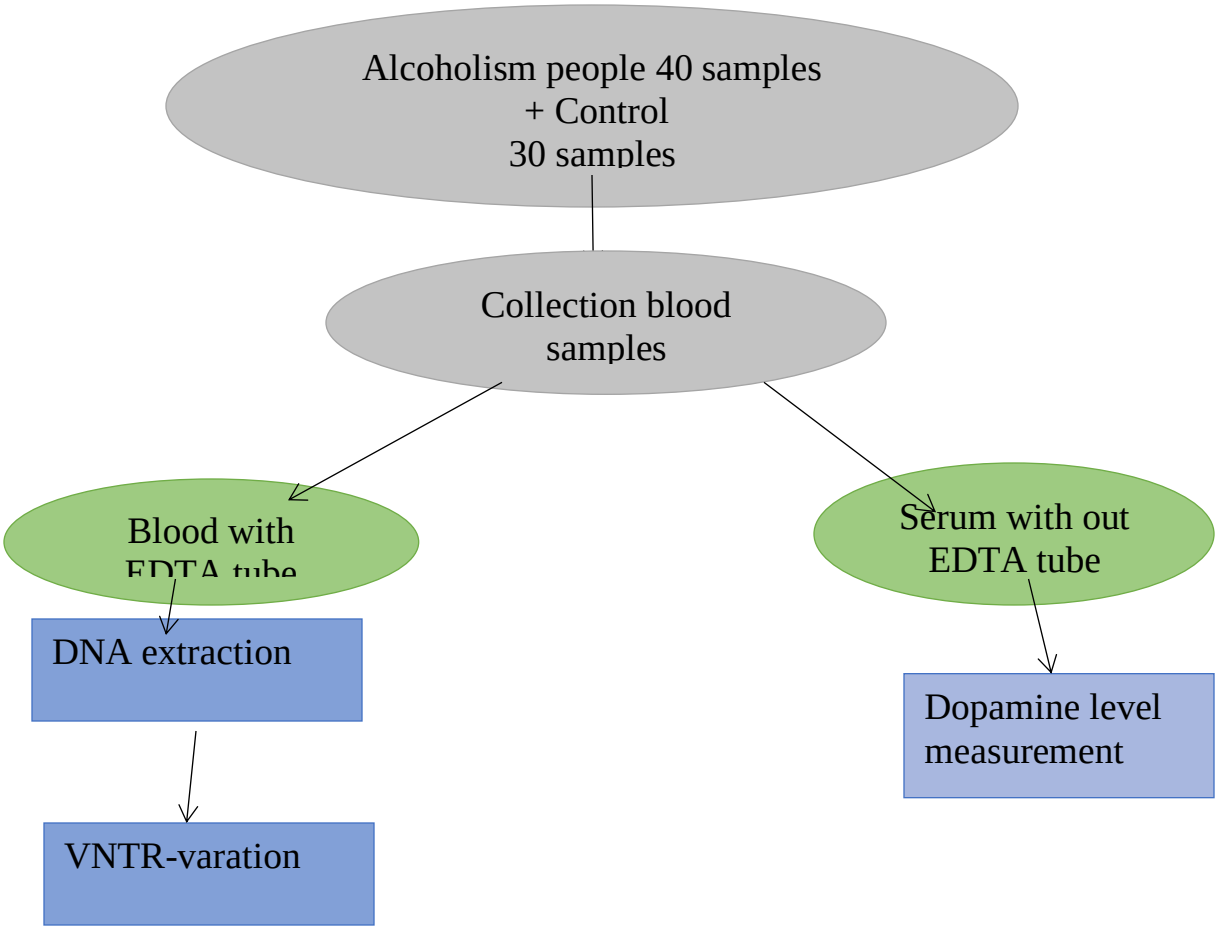


Figure (3-1): Scheme experiment design.

3.3: Study subjects

Case-control study was conducted 20\6\2021 to 27\8\2021 on (40) alcoholism person's whom taken to the hospital to measure the level of alcohol in their blood by sending their samples to the Institute of Forensic Medicine and 30 healthy people as control so we used them as a samples to calculate the dopamine concentration and the gene VNTR D1A and its effected by alcohol in alcoholism in Babylon city- Iraq.

3.4: The methods

3.4.1: Blood collection

1-About five milliliters of venous blood were collected from each subject in the study.

2-The blood was separated as 1ml into EDTA tubes used for genetic analysis.

3- then 4 ml of blood centrifuged to get serum and then collected in plain tube.

4- then all samples stored at – 80 ˚C (deepfreeze) in order to be used later in analysis of the study.

3.4.2: Body Mass Index

Body mass index (BMI) was calculated using the formula BMI = weight(kg)/ height2 (m2) and classifying underweight (BMI < 18), normal (BMI 18-24.9), overweight (BMI 25-29.9), obesity (BMI 30-39.9) and morbid obesity (BMI > 40) (WHO, 2004).

3.4.3: Human dopamine assay

The dopamine was determined according to leaflet of kit as fallowing:

1-All solutions was prepared in room temperature.

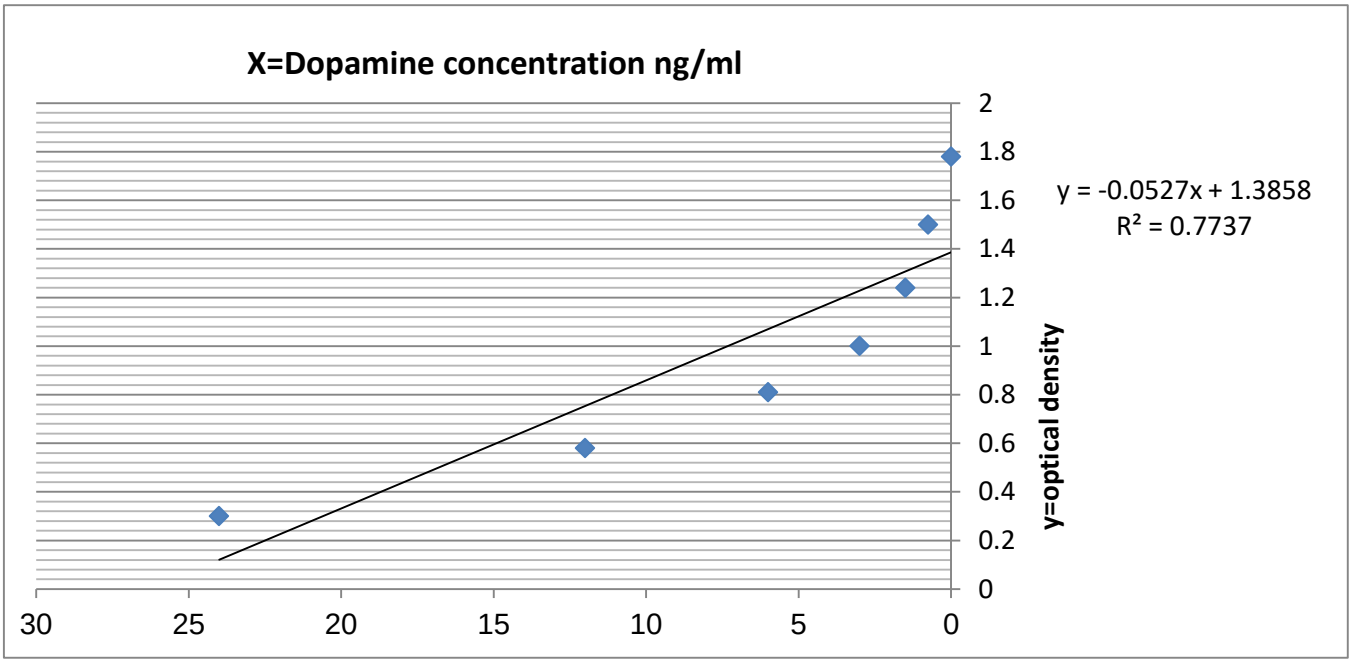
2-About 50 and 40 µl of standard and sample was added to standard and

sample well separately, then 10 µl anti-DO antibody was added to sample well, meanwhile 50 µl streptavidin-HRP was added to both sample and stander well with mixing.

3-Incubation at 37 ˚C for 60 min.

4- Washing was implemented by 350 µl wash buffer for 5 times.

5-Substrate solutions (A and B) was added in volume 50µl with incubation 37 ˚C for 10 min in the dark.



Fig(3-2) stander curve of human dopamine ng /ml

3.4.4: Genetics study (DNA Extraction)

Genomic DNA from white blood cells (WBCs) for both drunker and control group were extracted by using DNA extraction kit (G-spin) as described below:

1-About 200 µl of blood was added to a 1.5 ml micro centrifuge tube.

2-About 30 µl of Proteinase K (10 mg/ml) was added to the 1.5 ml

micro centrifuge tube and mixed briefly. The mixture is incubated at 60ºC for 15 minutes.

3-About 200 µl of BL Buffer was added to the 1.5 ml micro centrifuge tube and mixed by shaking vigorously.

4-The mixture was incubated in a 60ºC water bath for 15 minutes. During incubation, the tube was inverted every 3 minutes.

5-About 200 µl of absolute ethanol was added to mixture with gently mixing.

6-The mixture transfer to GD column and centrifuged for I min at 15000 rpm.

7-Filtrated was discarded, and 700 µl of Buffer WB was transferred to the same column, next centrifuged at 15000 rpm for 1 min. then centrifugation again for 3 min.

8-About 100 µl of dH2O were added to column and left for 2 min, then centrifugation for 2 min to eluted DNA.

3.4.5: Reconstituting and diluting primers

Primer was constructed by Pioneer in a clean room under strict ISO9001:2000 to confirm DNase/RNase and DNA free environment. Pioneer ®primers were commonly shipped in a lyophilized state. The units of a lyophilized primer were given as a mass, in Pico moles. To create a stock of primers, one would reconstitute the primer in sterile 1X TE (1 mM Tries, 0.1mM EDTA, pH 8.0) or sterile, nuclease-free H2O. The company supplied the amount of TE or sterile, nuclease-free H2O to be added to each primer to obtain master stock that would be used again to obtain a working stock.The following steps were followed for reconstituting and diluting the primers:

1-Spin down the tube before opening the cap.

2-Add the desired amount of water according to the oligos manufacturer to obtain a 100 pmoles/µl (Master Stock).

3-Vortex properly for re-suspend the primers evenly.

4-Transfer 10 µl of the master stock to a 0.2 ml eppindorff tube that contains 90 µl of sterile, nuclease-free H2O (Working Stock).

5-The master stock was stored at -20 C°.

6-The working stock was stored at -20 C°.

7-The working stock was thawed on ice and vortex before using in PCR and then stored at -20 C°.

Table (3-3): Sequences of primers used for PCR amplification of, DAT1 – VNTR

DNA Primer	Sequences	Amplicon size (kb)	References
DAT1 VNTR Polymorphism (Cleaver Scientific /UK) apparatus.	**F:5'- TGTGGTGTAGGGAACGGCCTGA-3' R: 5'CTTCCTGGAGGTCACGGCTCAAGG3' GTC Series thermo cycler**	VNTR 11 repeats (520pb), VNTR 10 repeats (483pb)	(Glavina Jelaš et al.,2018)

3.4.6: Polymerase chain reaction amplification analysis

PCR optimization was done as a first step using a gradient temperature ranging from 49 ˚C to 62.1˚C. After the determination of optimum annealing temperature (57.8 ˚C), the PCR reaction mixture consisted of < 250 ng template DNA, 400 µM of each dNTP, 12.5 µl buffer of 1 U GoTaq DNA polymerase (Promega), 10 µM of each primer and 3 mM MgCl2 in 25 µl of total reaction volume.

Amplification reactions were carried out by using GTC Series thermo cycler (Cleaver Scientific /UK) apparatus.

After determination of the optimum annealing temperature the following program was set in the thermo cycler to amplify the target DNA fragments.

Table (3-4): The PCR conditions used for DAT1-VNTR polymorphism amplification.

Stage	Temp.(CO)	Time(min)	Function	Cycles
1	95	2:00	Initial denaturation	1
2	95	1:00	Denaturation	30
	57.8	1:00	Primer annealing	
	72	1:00	Template elongation	
3	72	10	Final elongation	11
4	4	-	Incubation	Hold

3.5 Statistical Analysis

All statistical analysis were performed by using SPSS 23 version. Data were expressed as (mean ± SE) by using T-test. The normality of the distribution of all variables was assessed by the students ANOVA test and Pearson correlation analyses that have been used to determine the significant difference among the groups. P values less than (0.05) is considered significant. Statistical Methods and their Applications. January 2011Publisher: FPV UKF v Nitre ISBN: 978-80-8094-807-8

4. Result and Discussion

4.1: The baseline characteristics and alcohol level of study groups

The socio demographic distribution of study parameters were exhibits in table (4-1).

Variables	drunks	control	sig
Age	29.8750±1.43500	26.7667±0.80898	.089
BMI	26.6977±0.56971	24.4970±0.68664	.016
Duration	3.8500±0.43346	-	-
Alcohol level	74.2750±6.50453	0	-
Independent t test , p<0,05			

Table (4-1) the baseline characteristics and alcohol level of study groups.

4.1.1: The distribution of study groups according to age categories

The distribution of study groups according to age categories show that the first categories shows that less than 30 years 55% at drink was compares with controls 63.33% and for more than 30 years for drunks was 45% compares with controls in which percentage 36.66%.

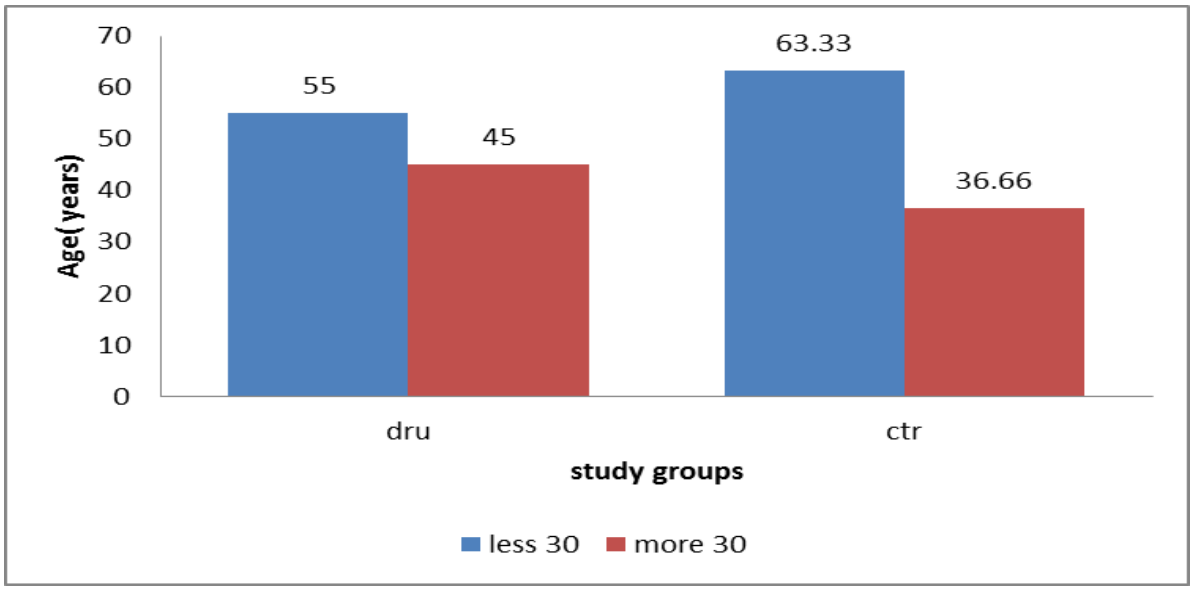


Figure (4-1) distribution of study groups according to age

Alcohol consumption is a lifestyle behavior that has been extensively studied for potential benefits and risks to health (Thun *et al*., 1997). It has been suggested that older persons may be at increased risk of adverse consequences of alcohol because of a diminished volume of distribution for alcohol due to a decrease of lean body mass (Vestal *et al*., 1976). Marsha et al.,(2001) repotted by them study that four age categories (45–49, 50–54, 55–59, and 60–64 years) were used in the evaluation of the association. The proportion of drinkers and, among drinkers, the amount of alcohol consumed.

Excessive alcohol consumption during adolescence represents a concern due to its numerous negative consequences –difficulty in emotional regulation, increased risky sexual behaviors, fighting and physical aggression, neurotoxic effects on memory, attention and learning, and changes in brain structures and their functionality (Bajac *et al*, 2016). In Spain, 1 out of 3 students aged 14-18 years acknowledged having engaged in this type of consumption drugs (Simöes et al., 2018). During pre-adolescence (around age 11) differences are barely perceptible and increase with age (Goldstein et al. 2013; Kuntsche *et al*., 2015).

4.1.2: The distribution of the study group by Body mass index (BMI).

Three categories of BMI were dependent in present study, less than 30 (40%) and more than 30 (17,5%) kg/m2 and(42%) for over weight 25 – 29,9 kg/m2 in alcoholism's in compare with control group figure (4-2).

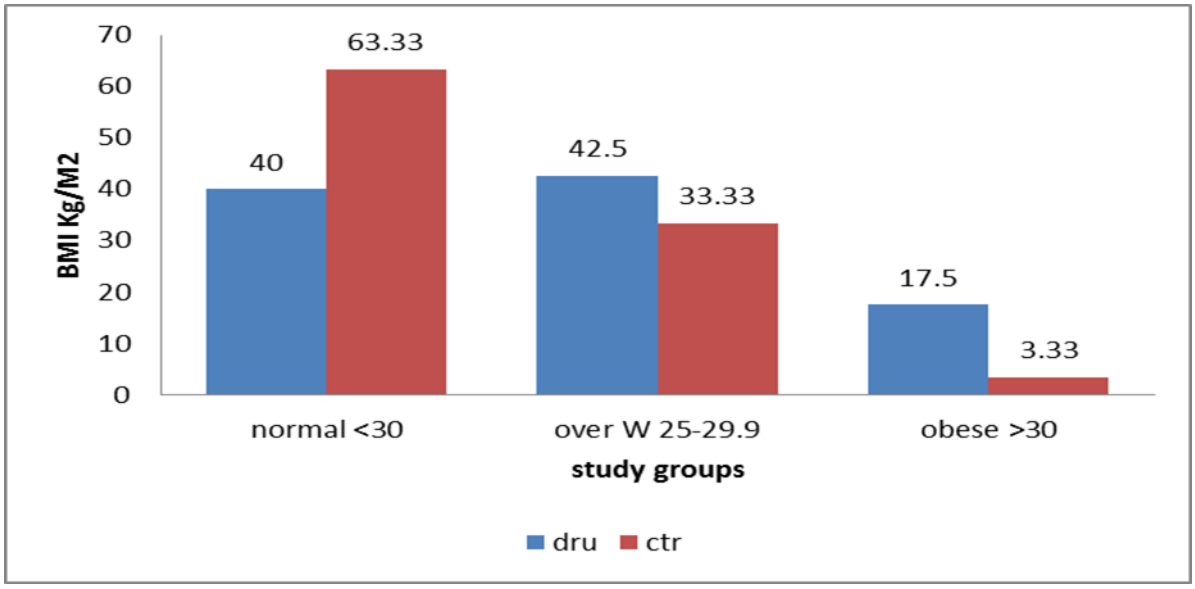


Figure (4-2) distribution of study groups according to BMI kg/m^2

The amount and frequency of alcohol consumed have been found to correlate with BMI. The binge drinkers and the heavy drinkers often had a significantly higher BMI than those who participated in only light-to-moderate drinking. The National Institute on Alcohol Abuse and Alcoholism's (NIAAA, 2007). Using national surveys in the United States examined quantity, frequency, and average volume to categorize alcohol consumption based upon participant information. They found that people who consumed four or more drinks per day had significantly higher BMIs than those who consumed one drink per day (Mary *et al*., 2012).

Alcohol is high in calories, so drinking alcohol may contribute to higher BMIs and the poor health choices of college-age students who are already overweight, particularly freshmen female students who drink four or more drinks per day and male students who consume five or more drinks per day. Elevated triglycerides and low high-density lipoprotein cholesterol levels are the result of continued high carbohydrate intake, especially if students are already overweight when they first start to drink (Park *et al*., 2003).

4.1.3: The distribution of study groups according to home

The distribution of study groups according to home the percentage of drinking peoples (17.5%) in rural and (82.5%) urban fig (3-4).

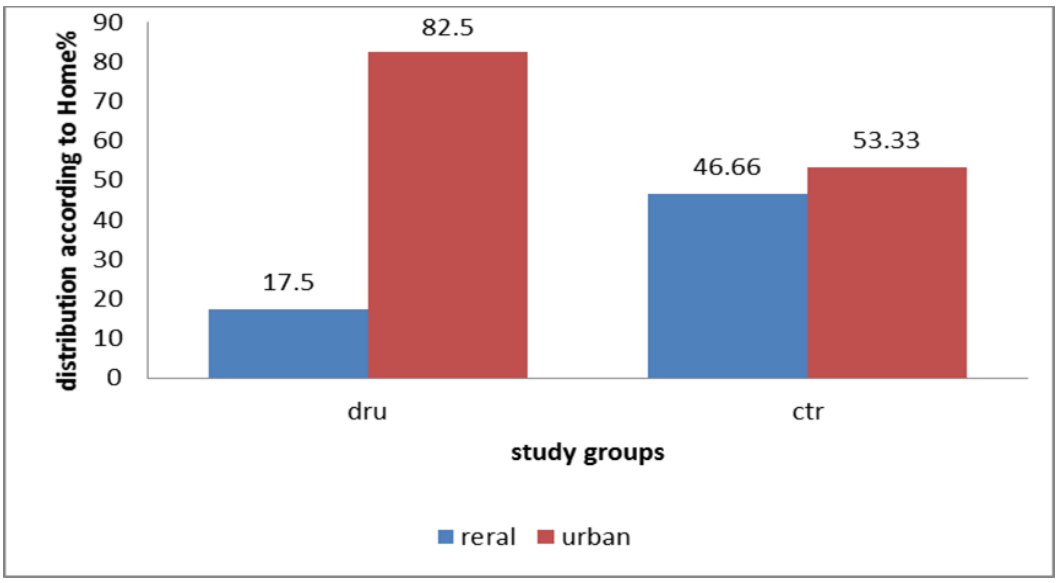


Figure (4-3) distribution of study groups according to home

A number of social and cultural factors predict increased alcohol use, including discrimination and its related stigma. The role of discrimination and stress in health-related risk behaviors, including alcohol use, is well established (Dawson *et al*. 2005; Hatzenbuehler 2009).

The stress and coping framework frequently is applied to explain the influence of discrimination and stigma on health (Pascoe and Smart Richman 2009).

For example, socioeconomic status (SES) indicators (i.e., education, income, and occupation) usually are strong predictors of health behaviors and outcomes and tend to be positively associated with health. People with higher SES tend to drink more frequently than others (Huckle *et al*. 2010). Among drinkers, low-SES groups tend to drink larger quantities of alcohol (Huckle *et al*. 2010). Like other health issues, alcohol use can be linked to a complex array of factors ranging from individual-level (i.e., genetics) to population-level (i.e., cultural and societal factors) characteristics (Berkman *et al*. 2000).

On a population level, emerging research has documented the relationship between social determinants and health (Berkman and Kawachi 2000; Berkman et al. 2000) and, specifically, the social epidemiology of alcohol use (Bernstein et al. 2007; Galea *et al*. 2004). Social capital theory suggests that social networks and connections influence health (Berkman *et al*. 2000). Individuals who have higher levels of social support and community cohesion generally are thought to be healthier because they have better links to basic health information, better access to health services, and greater financial support with medical costs. (Berkman and Kawachi 2000).

The reason for the high rate of alcoholics in cities compared to rural areas may be due to the nature of life in the city in terms of multiple relationships and sometimes the level of economic income.

4.1.4: The distribution of drunks according to criminal behaviors

The fig (4-4) show the distribution of drunks according to criminal behaviors 60% violent,17% normal drink,12% paraphilia's, 8% drunk with possession of a drunk and 3% accident.

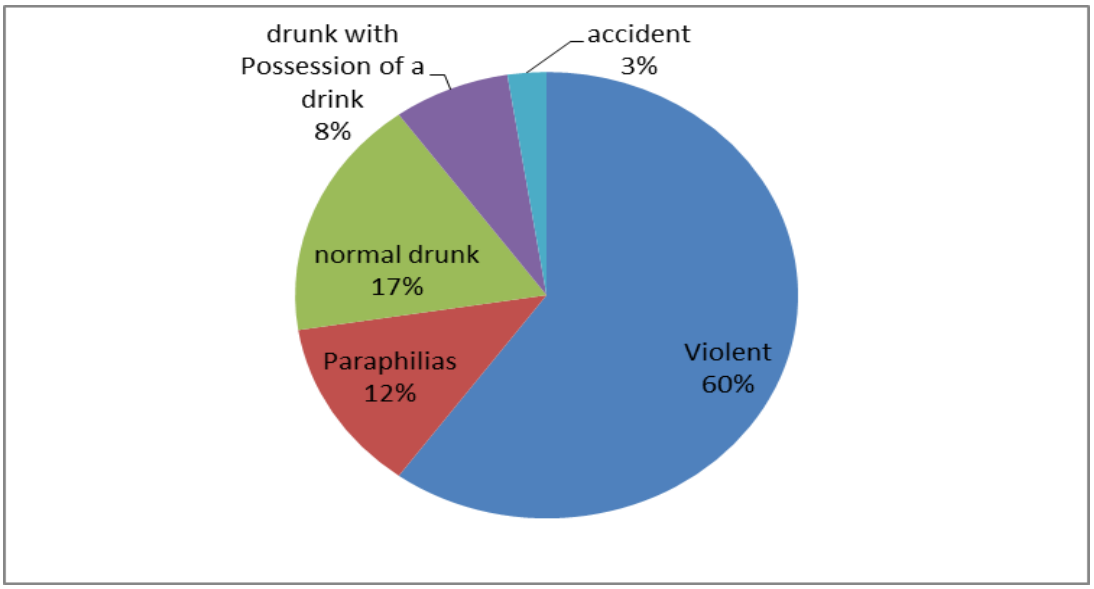


Figure (4-4) distribution of drunks according to criminal behaviors

The present study makes an important and timely contribution to our understanding of the effects of alcohol use on criminal activity among adolescents and young adults.

Alcohol use is often connected with criminal activity for both perpetrators in a more recent study, heavy drinkers were 2.67 times more likely to be shot during an assault than nondrinkers (Branas *et al*., 2009). Alcohol use, delinquency, criminal activity, and other risk-taking behaviors are more prevalent during adolescence (Arnett, 1992) and adolescents and young adults contribute to a large proportion of all arrests. According to a report from the U.S. Department of Justice, 44.4 percent of all persons arrested for criminal offenses in the United States in 2006 were under 24 years of age (Pastore and Maguire, 2006).

Moreover, adolescents have less impulse control and might be more vulnerable to problematic alcohol use than adults. Since the human brain continues to develop until an individual is in his or her early twenties, excessive alcohol use may have a more severe and long-lasting effect when consumed during adolescence. Given the risks that heavy drinking poses to adolescents and the overwhelming costs of criminal activity to society, it is important to identify the ways in which alcohol contributes to violence Branas *et al*., 2009).

Several theories attempt to explain the co-occurrence of drinking and criminal activity. First, the pharmacological properties of alcohol might impair potential perpetrators' higher-level cognitive processes and increase the likelihood of aggressive behavior (Giancola, 2000) .Individuals who consume alcohol may be more likely to place themselves or their property in situations that increase the likelihood of being victimized and second, expectations about alcohol's presumed effects could also lead to aggression, as seen in experimental studies in which the belief that one has consumed alcohol leads to violent behavior (Zimmerman and Benson, 2007; Carpenter and Dobkin, 2010).

4.1.5: The distribution of drunks according to duration of abuse

The fig (4-5) show the abuse according to duration 65% where < 5 years ,30% of abuse between 5-10 years and 5% where > 10 years of abuse .

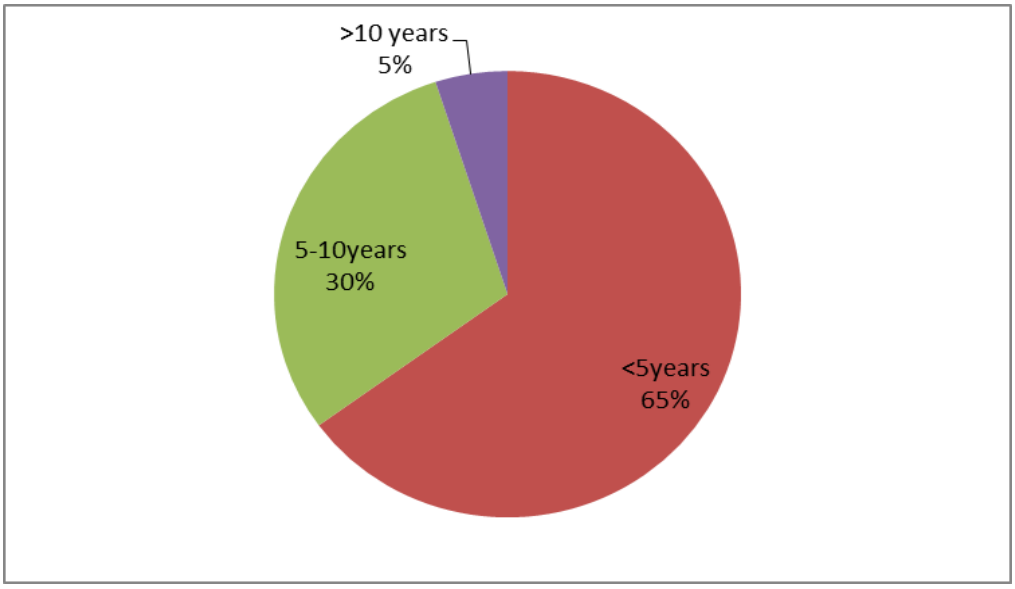


Figure (4-5) distribution of drunks according to duration of abuse

Alcohol is one the most widely used and abused drugs in the world and the number of annual alcohol-attributed deaths exceeds 3 million (WHO,2014). Drugs of abuse, including alcohol, increase dopamine release in the striatum (WHO,2018).

The World Health Organization has estimated that as of 2016, there were 380 million people with alcoholism worldwide (5.1% of the population over 15 years of age) (WHO,2018). As of 2015 in the United States, about 17 million (7%) of adults and 0.7 million (2.8%) of those age 12 to 17 years of age are affected (Cherpitel,2007; Littrell ,2014). Alcoholism is most common among males and young adults. Geographically, it is least common in Africa (1.1% of the population) and has the highest rates in Eastern Europe (11%),The International ISBN Agency(WHO,2018). Alcoholism directly resulted in 139,000 deaths in 2013, up from 112,000 deaths in 1990(Littrell ,2014) . A total of 3.3 million deaths (5.9%

of all deaths) are believed to be due to alcohol(WHO,2018). Alcoholism reduces a person's life expectancy by approximately ten years (Schuckit MA (2014).

4.2: The dopamine ng/ml concentrations differences in study groups

The concentration of dopamine in alcohols drinking peoples 4.29 ± 0.27 is less than controls peoples 8.7 ± 0.22 as show in fig (4-6).

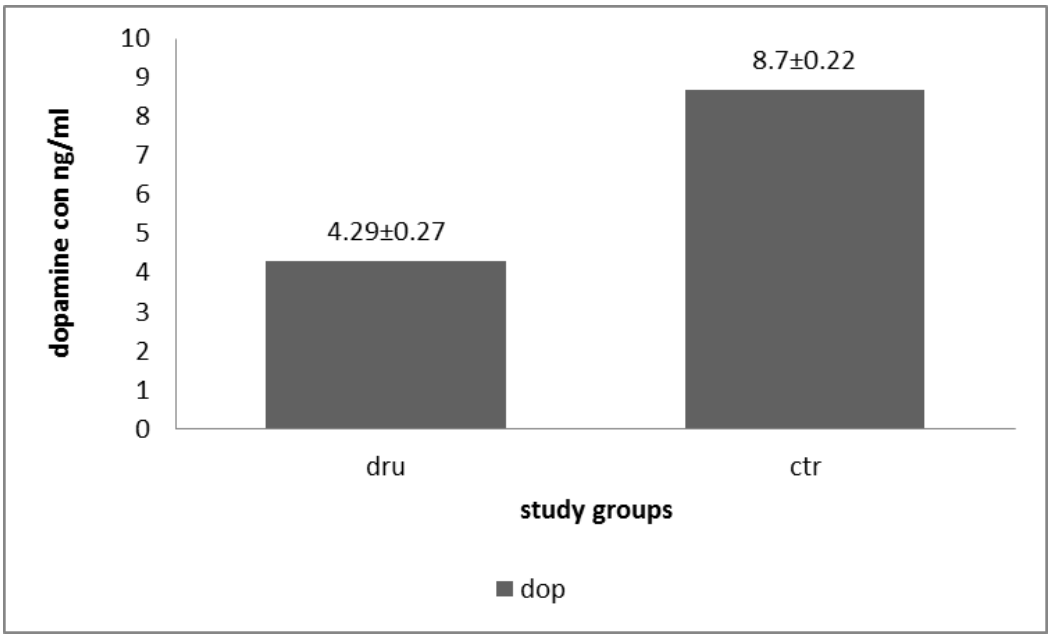


Figure (4-6) the dopamine ng/concentrations differences in study groups (independent t test at $p<0.05$).

During drug withdrawal, the brain of an addict has significant deficits in dopamine function associated with deficits in the prefrontal regions. Since dopamine is additionally involved in the reinforcing effects of natural reinforcers, it has been suggested that this fluctuation in brain dopamine function subsequently decreases the sensitivity of natural reinforcers (Katie *et al*.,2004).

Chen *et al*.,(2007) identified a wide range of neurotransmitters related to alcohol metabolism including dopamine, 5-HT, γ-amino butyric acid, glutamate, endogenous opioid transmitter, acetylcholine and norepinephrine. Yoshimoto et al.,(2000) reported a dose-related elevation of extracellular DA levels in the

amygdala after intraperitoneal injection of ethanol and a delayed elevation of DA after ethanol injection in the central amygdaloid nucleus via a microdialysis membrane.

It is believed that alcohol effects on the brain produce different outcomes than in alcohol naive states (Jimenez and Grant,2017). It is achieved by the volitional consumption of alcohol (to intoxication) for a long time period (>1 year). This time scale allows for long-term examination of drinking behavior and, eventually, ex vivo analysis of the long-term consequences of AUD on neurobiological processes, including dopamine release. AUD involves dysfunction of several brain regions, including ventral and dorsal striatal areas rich in dopamine neurotransmission (Yin and Knowlton,2006). Acute alcohol increases dopamine release across the striatum primarily due to increased firing of midbrain dopaminergic neurons, an effect that may underlie the initial reinforcing properties of alcohol. In individuals that drink alcohol frequently, however, tolerance develops, and more alcohol is consumed. Concomitantly, adaptations in glutamatergic, GABAergic, and dopamine transmission occur (Vena and Gonzales,2015) and greater or continued amounts of alcohol can result in allostatic changes to preserve normal brain function (Melis *et al*.,2005; Koob,2008).

Armando et al.,(2021) found that long-term alcohol consumption altered dorsal striatal dopamine release and uptake in a sex- and subregiondependent manner and the regulation of dopamine release by D2/3 dopamine autoreceptors was altered by long-term alcohol consumption in male, but not female, rhesus macaques regardless of abstinence status

4.2.1: The dopamine and alcohol levels in drunks according to age categories

The dopamine concentration of study groups according to age categories show that the first categories less than 30 years ware 3.90±0.28627 ng/ml and 4.77±0.49861 ng/ml more than 30 years ware There was no significant difference between age , dopamine and alcohol concentration at heavy drinker table (4-2).

Variables	Dopamine ng/ml	Alcohol mg/cm3

Age categories		
<30	3.90±0.28627	69.04±8.38610
>30	4.77±0.49861	80.66±10.25396
Sig	0.121	0.381
Independent t test , p<0,05		

. **Table (4-2) the dopamine and alcohol levels in drunks according to age categories**.

Drugs of abuse, including alcohol, increase dopamine release in the striatum (Di Chiara and Imperato ,1988). Alcohol use among adolescents is heterogeneous, ranging from low, normative use to heavy, pathological use. Alcohol is the most frequently used substance, as it is generally the easiest for adolescents to access (WHO.2018). The average age of initiation for alcohol use among US and Australian adolescents is 15 years (Richmond et al.,2017;Aiken *et al*.,2018). Across Europe, most adolescents begin drinking alcohol between ages 12 and 16, with 25% of adolescents in this region first consuming alcohol by age 13 (WHO, 2002–2014. 2018). The worldwide estimate of adolescents (age 15–19) who drank alcohol in the past month is 27%, ranging from 1 to 44% across countries. Higher rates of past month adolescent drinking occur in higher income countries; the highest rates are observed in the European region (44%), and the lowest rates are observed in the Eastern Mediterranean region (1.2%; 33, 37). Past month alcohol use among adolescents in other countries ranges from 38% in the Americans and Western Pacific regions, to 21% in Africa and Southeast Asia, and 14% in Japan (Morioka *et al*,2013; WHO,2018).

4.2.2: The dopamine and alcohol levels in drunks according to BMI categories

The dopamine concentration of study groups according to BMI categories show that the first categories less than 25 ware 4.4125±0.44167 ng/ml and 4.9857±0.6783 ng/ml more than 30 ware non signefent table (4-3).

Variables	Dopamine ng/ml	Alcohol mg/cm3
BMI		
<25	4.4125±0.44167	82.50±12.89477
25-29.9	3.8941±0.42456	69.2941±8.24120
>30	4.9857±0.6783	67.57±11.755
Sig	0.374	0.596
ANOVA one way p <0.05		

Table (4-3) the dopamine and alcohol levels in drunks according to BMI categories,

The most impressive findings have shown that the reinforcing effects of frequently abused drugs are associated with large and rapid increases in dopamine (Volkow et al.,2003). Pirola and Lieber (1972) reported on the hypermetabolic effect of alcohol more than thirty years ago, however this applies only to higher consumption rates (Pirola and Lieber ,1972, 1976; Hodgkins et al.,2004). In their study, Pirola and Lieber found that when a group of alcoholics had fifty percent of carbohydrate calories replaced with ethanol, a small but significant decrease in body weight was noted (Pirola and Lieber ,1972).

4.2.3: The dopamine and alcohol levels in drunks according to Home categories

The dopamine concentration according to home the drinking peoples 5.071±0.83115 ng/ml in rural and 4.1273±0.28753 ng/ml in urban as show in table was non-significant table (4-4).

Variables	Dopamine ng/ml	Alcohol mg3/cm3
Home		
Rural	5.071±0.83115	57.00±10.54017
Urban	4.1273±0.28753	77.939±7.462
Sig	0.203	0.226
Independent t test , p<0,05		

Table (4-4) the dopamine and alcohol levels in drunks according to Home categories.

A number of social and cultural factors predict increased alcohol use, including discrimination and its related stigma. The role of discrimination and stress in health-related risk behaviors, including alcohol use, is well established (Dawson et al. 2005; Hatzenbuehler 2009).

4.2.4: The dopamine and alcohol levels in drunks according to duration of abuse categories

The dopamine concentration according to duration of abuse show the drinking peoples that less than 5years ware 4.06±0.28550 ng/ml and more than 10 years ware 1.9000±0.700 ng/ml was signefent rather than alcohol level non-significant as show in table (4-5).

Variables	Dopamine ng/ml	Alcohol mg/cm3
Duration		
<5	4.06±0.28550	65.07±7.20596
5-10 years	5.1917±0.58367	86.9167±12.09461
>10	1.9000±0.700	118.00±50.0
Sig	0.022	0.093
ANOVA one way p<0.05		

Table (4-5) the dopamine and alcohol levels in drunks according to duration of abuse categories.

Acute alcohol increases dopamine release across the striatum (Koob and Volkow ,2010 ; Vena and Gonzales,2015) In individuals that drink alcohol frequently, however, tolerance develops, and more alcohol is consumed. Concomitantly, adaptations in glutamatergic, GABAergic, and dopamine transmission occur (Abrahao *et al*.,2017) and greater or continued amounts of alcohol can result in allostatic changes to preserve normal brain function. Armando et al.,(2021)found that regulation of dopamine release by D2/3 dopamine autoreceptors was altered by long-term alcohol consumption in male, but not female.

The AUD is a chronic relapsing brain disease. One factor contributing to the development of AUD may be the change in synaptic signaling in the caudate and putamen that could contribute to a bias toward sensory-motor circuit control of behavior and inflexible alcohol consumption (Corbit et al.,2012 ; Gremel and Lovinger, 2017).

4.2.5: The dopamine and alcohol levels in drunks according to criminal behaviors categories

The dopamine and alcohol concentration according to criminal behaviors categories showed. non-significant as show in table (4-6)

Criminal behavior	**Dopamine ng/ml**	**Alcohol mg/cm3**
Violent	4.1625±0.378	76.2917±8.83
Paraphilia's	3.8400±0.416	67.0000±10.52
normal drunk	4.3857±0.85	74.8571±18.66
drunk with Possession of a drink	5.7000±0.17321	48.6667±1.33
Accident	4.8000±0	135.0000±0
Sig	0.645	0.240
ANOVA one way p<0.05		

Table (4-6) the dopamine and alcohol levels in drunks according to criminal behaviors categories.

Neurotransmitter systems, which transmit chemical signals across synapses, also undergo significant change in adolescence. Dopamine projections to the limbic and frontal regions often peak during adolescence (Spear ,2011;Ernst,2014). Neurotoxin exposure, particularly alcohol use, during adolescence can affect healthy brain development, with even minor changes in neurodevelopmental trajectories affecting a range of cognitive, emotional, and social functioning (Lees et al.,2019). Alcohol use during adolescence could therefore set the stage for cognitive problems into adulthood, conferring functional consequences throughout life.

4.2.6: Correlation between dopamine levels and alcohol levels

When study the correlation between dopamine levels and alcohol levels, non- significant invers correlation fig (4-12)

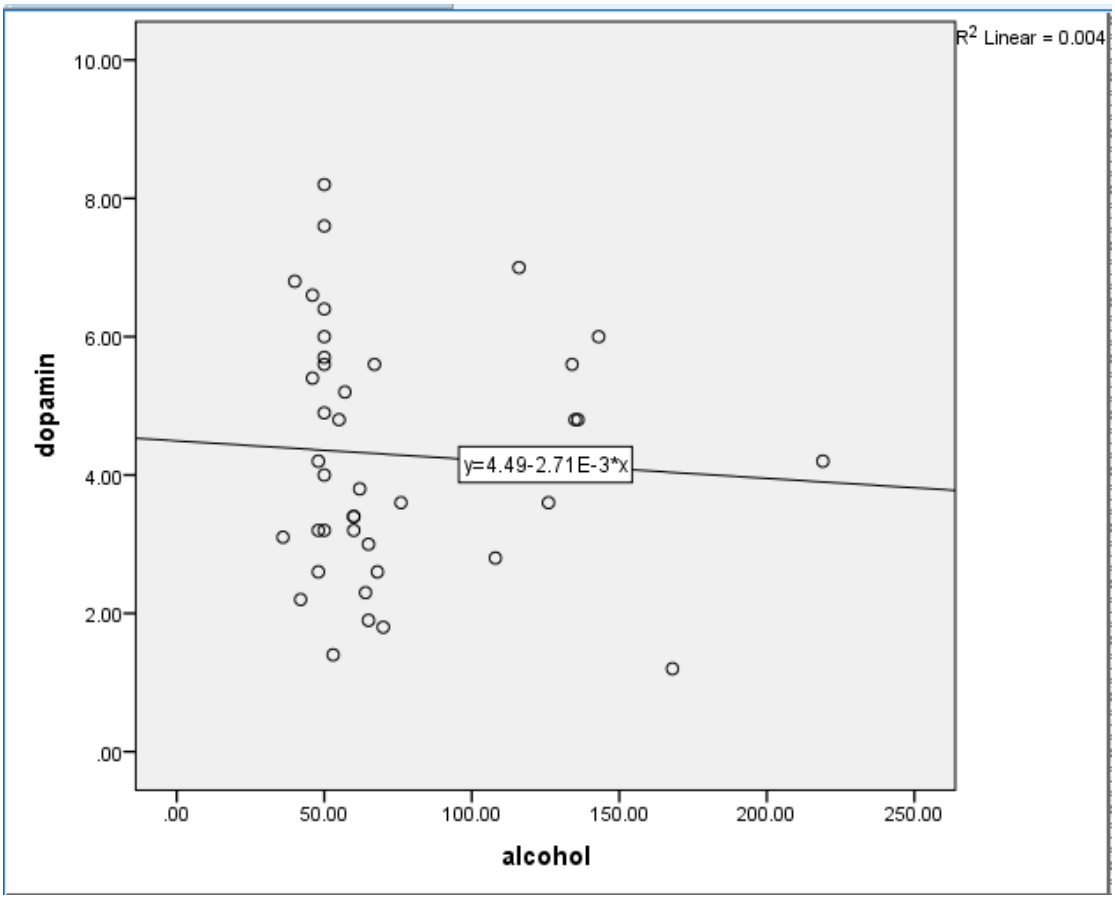


Figure (4-7) correlation between dopamine levels and alcohol levels, non-significant invers correlation (r -0.063, P 0.698).

4.3: *DAT1 VNTR* Polymorphism Genotyping of alcohol drinking

The electrophoresis pattern of dopamine gene *VNTR* gene polymorphisms in study groups showed in fig(4-7).

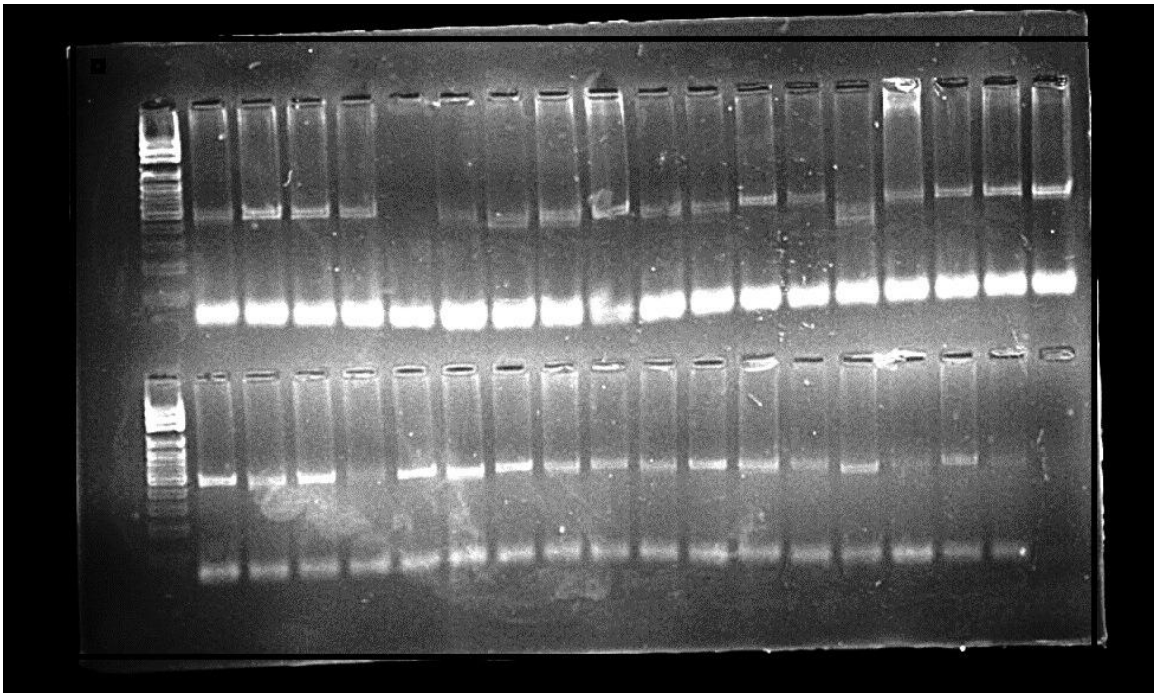


Figure (4-7): The electrophoresis pattern of PCR product for *DAT1 VNTR* Polymorphism gene this amplification product of band 520 bp, 483 bp for alcoholism's .1% agars , 75V, 20Am for 1h. Lane 1-5 PCR product of alcoholism's.

Three repeat sequences appeared (11,10 and Deletion) in the alcoholics and the control samples and its compression was non-significant table (4-7) ,

Table (4-7) genotyping of dopamine *gene VNTR* in drunks and control group

Dopamine VNTR	**drunks**	**control**	**Odd ratio (CI%)**	**Sig**
11	30	26	0.4196 0.1191 to 1.4779	0.1764
10	8	3	8.0000 0.5804 to 110.2735	0.1203
Deletion	2	1	2.3333 0.0298 to 182.9241	0.7034

Three repeat sequences appeared (11,10 and deletion) for the control group, it was significant, while the variation was not significant in the alcoholic drinker table (4-8)

Dopamine VNTR	**drunks**	**control**
11	4.2933±0.29892	8.6923±0.23310
10	3.7000±0.70711	8.8000±1.11355
Deletion	6.0333±0.82529	8.6000±0.00
Sig	0.142	0.006
ANOVA one way p<0.05		

Table (4-8) genotyping of Dopamine *gene VNTR* effect in the dopamine level of drunks and control group

Alcohol use disorder (AUD) has a strong genetic component with heritability estimates of about 50% (Oroszi and Goldman, 2004). AUD is polygenetic, with many genes likely contributing to AUD risk in different individuals, in different ways, and in interaction with the environment (Buhler *et al*., 2015).

It is well established that the central dopaminergic reward pathway is likely involved in alcohol intake and the progression of alcohol dependence. Dopamine transporter (DAT1) mediates the active re-uptake of DA from the synapse and is a principal regulator of dopaminergic neurotransmission. The gene for the human DAT1 displays several polymorphisms, including a 40-bp variable number of tandem repeats (VNTR) ranging from 3 to 16 copies in the 3'-untranslated region (UTR) of the gene(Lakkakula *et al*.,2012).

In alcoholic individuals, the dopamine D2 receptor (DRD2) gene on chromosome 11 (q22-q23) has been linked to higher alcohol use via mechanisms involving incentive salience attributions and desire (Pushplata et al.,2010).

Conclusions & Recommendations

Conclusions

From present study we can concluded that:

1-The dopamine level was lower in the alcoholic drinkers compared to the control

2-The percentage of alcoholic drinkers in the city is higher than in the countryside.

3-Three repeat sequences appeared (11,10 and deletion) for the control group, it was significant, while the variation was not significant in the alcoholic drinker.

4- the duration of alcohol consumption effect on dopamine concentration for alcoholism and criminal behavior .

Recommendations

1- Conducting a study of a larger sample of the population with the use of other factors or other hormones and studying other genetic variations.
2- Conducting a study that includes drug users and making a comparison between the types.
3- Used other technologies like RT-PCR.
4- Cooperate with forensic institution to get more information and to put farther investigation which serve the forensic science ,

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CLONINGER'S TEMPERAMENT AND CHARACTER DIMENSIONS AND DOPAMINERGIC GENES: DAT1 VNTR AND COMT VAL158MET POLYMORPHISMS

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Statistical Methods and their Applications. January 2011 Publisher: FPV UKF v Nitre ISBN: 978-80-8094-807-8

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الخلاصة

من الواضح أن شرب الكحول له تأثير مهم على السلوكيات الاجتماعية ، مثل زيادة العدوانية ، والإفصاح عن الذات ، والمغامرات الجنسية ، وما إلى ذلك. ضعف لذلك تحاول الدراسة الحالية إيجاد صلة بين مستوى الدوبامين والسلوك العدواني لشارب الكحوليات.

أجريت الدراسة خلال الفترة من 20 \ 6 \ 2021 إلى 27 \ 8 \ 2021 على (40) شخص مدمن على الكحول تم نقلهم إلى المستشفى لقياس مستوى الكحول في دمائهم عن طريق إرسال عينات هناك إلى مؤسسة الطب الشرعي. و 30 اصحاء كمجموعة تحكم (رجال فقط) بمتوسط اعمار (20-55 سنة) في مدينة بابل - العراق.

عند دراسة مقارنة توزيع الفئات العمرية بين شارب الكحول والمجموعة الضابطة ، وجد أن أقل من 30 عامًا كان 55٪ عند الشرب و 63.33 في المجموعة الضابطة. أكثر من 30 عامًا كان 45٪ عند الشراب مقارنة بـ 36.66 عنصر تحكم. وكان مؤشر كتلة الجسم أولًا أقل من 30 (40٪) كجم / م 2 عند السكر مقارنة بـ (63.33) كجم / م 2 وأكثر من 30 (17.5٪) كجم / م 2 في إدمان الكحول مقارنةً مع (3.33) كجم / م 2 التحكم مجموعة.

| وجد أن مدة تعاطي الكحول لا تعطي معنويا لمستوى الدوبامين والكحول حسب المتغير اقل من 5 سنوات و 5 - 10 سنوات واكثر من 10 سنوات.

وتبين أن نسبة الشرب في الريف (17.5٪) أقل من الحضر (82.5٪).

كشفت الدراسة الحالية أن السلوكيات الإجرامية كانت 60٪ عنيفة ، 17٪ مشروب عادي ، 12٪ مشاغبين ، 8٪ في حالة سكر مع حيازة مخمور و 3٪ حادث.

عند دراسة مستويات الدوبامين لمن يشربون الكحول ، أوضحت الدراسة أن تركيز الدوبامين في الأشخاص الذين يشربون الكحوليات 4.29 ± 0.27 أقل من الضوابط لدى الأشخاص 8.7 ± 0.22 ولم يكن هناك فرق كبير بين العمر وتركيز الدوبامين والكحول على طاولة الشراب الثقيلة وكذلك في مؤشر كتلة الجسم تعاطي الشرب والسلوك الإجرامي. تأثير المدة على تركيز الدوبامين وجد أن أقل من 5 سنوات كان 4.06 ± 0.28550 و 5-10 سنوات 5.1917 ± 0.58367 و> 10 سنوات كان 1.9000 ± 0.700 وهو يعطي معنويًا في الشرب الكحولي.

جمهورية العراق
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قسم علوم الحياة

تأثير تعدد الأشكال الجيني لمستقبلات د1 للدوبامين في السلوك الاجرامي لإدمان الكحول

بحث مقدم الى
مجلس كلية العلوم/جامعة بابل
وهو جزء من متطلبات نيل شهادة الدبلوم العالي في العلوم / الادلة الجنائية

من قبل

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اشراف

الأستاذ المساعد الدكتورة منى نجاح حسن علوان

1443هـ 2021م